POLITECNICO DI MILANO
Department of Electronics, Information and Bioengineering
Master of Science in Biomedical Engineering

Visuo-Haptic Model of Prostate Cancer Based on Magnetic Resonance Elastography: a Feasibility Study

Supervisor: Elena DE MOMI, PhD.
Foreign Advisor: Cristian LUCIANO, PhD.

Master Thesis of
Eleonora TAGLIABUE
Student ID: 854755

Academic Year 2016-2017

Summary

Prostate cancer (CaP) is not only a very common form of cancer, but also one of the main causes of cancer-related deaths among American men. Early detection of prostate cancer is key to increase the chances of a treatment able to preserve the healthy organs, limit side effects, and eventually improve survival rates.

Magnetic Resonance Elastography (MRE) is an innovative technique that images tissue stiffness distribution and provides as output a 3D map (the ”elastogram”) with quantitative elasticity values of the imaged areas. Prostate cancer has demonstrated to become harder than the surrounding healthy tissues, and can be therefore easily recognized on stiffness maps.

This thesis addresses the main limitations of the methods currently used for screening and early CaP diagnosis. Through the conjugation between MRE imaging and the possibilities offered by a Haptic Virtual Reality (HVR) environment we propose a non-invasive, accurate and complete tool that aims to improve the prostate cancer diagnostic process.

Information obtained from MRE has been employed to create a VR simulation of prostate cancer based on both visual and haptic cues, where the user can interact with a 3D virtual model of the patient’s prostate. The development of such an application has been possible thanks to the creation of a platform able to provide all the basic elements that allow to implement virtual reality-based simulations. *LACE library* is the result of this effort, and consists of a platform offering all the elements needed to conjugate robust graphics and haptics. Exploiting *LACE library* functionalities, a volumetric rendering of the color-coded tumor lesions (hard) as well as healthy (soft) tissues has been created. The surgeon can visually appreciate the whole patient anatomy from different perspectives, and recognize the lesions and their extent.

The main contribution of this work has been the implementation of a force feedback that relies directly on the MRE data and that allows to feel a distinctive difference in the resistance offered by regions with different stiffness. This was obtained by taking into account both the shear modulus of the currently touched point and the elasticity of the neighboring areas.

Haptic cues have been added with the purpose of enhancing visual information, based on the idea that the integration between more sensory modalities allows to increase the information content. The validity of this assumption has been tested by comparing users’ performances in locating hard masses through the simulator without and with the help of haptic feedback. Results show that when forces were active, participants were able to locate stiff regions with greater accuracy and in a smaller amount of time, with respect to when they performed the task with a version of the simulator lacking the forces.

Furthermore, qualitative evaluation of the visuo-haptic application has been conducted by a cohort of expert urologists. Results demonstrate an overall high satisfaction in the exploration of prostate anatomy through the simulator, and the possibility of a future introduction in the clinical practice.

By complementing a 3D model of the prostate based on MRE with haptic feedback, the developed approach would eventually lead to an early, precise, and exhaustive diagnosis of prostate cancer and has the potential to allow for a more accurate biopsy targeting as well as an improvement in pre-surgical planning phase.

1 Introduction

Prostate cancer (PCa) is the second most common cancer in men as well as the fifth leading cause of cancer-related deaths in men worldwide [1]. The main limitation of all the most common examinations for prostate cancer early detection, which include Digital Rectal Examination (DRE), Prostate-Specific Antigen (PSA) test and multiparametric Magnetic Resonance Imaging (mp-MRI), is that they are not able to provide accurate information about the actual presence, location and extent of tumor masses [2] [3]. Prostate biopsy is considered the gold standard for PCa detection but, since the exact location of the lesions cannot be known with precision at this stage, it is very difficult to accurately target a region with this procedure, meaning that PCa may remain undetected even if actually present [4]. Radical prostatectomy is the most effective treatment for prostate cancer. By removing the whole gland, this procedure should ensure that all tumors are taken away. Anyway, especially if the cancer was present on the sides of the organ, it could be able to spread outside of the gland, still leaving the patient at risk of recurrence [5]. If a diagnostic tool which allows to accurately identify the site of the tumor masses was available, it would help to improve both biopsy targeting and pre-surgical planning.

In this work, we present an innovative application that aims at helping urologists to accurately locate the disease in a non-invasive way, thus improving prostate cancer diagnostic process. It relies on Magnetic Resonance Elastography (MRE), an emerging imaging technique providing 3D maps of the quantitative elasticity values of the imaged areas, where PCa can be easily recognized. MRE images were used to obtain a 3D virtual model of the patient's prostate, with which the urologist can interact both visually and haptically. A volume haptic feedback algorithm has been implemented to facilitate hard masses localization, with the purpose of enhancing visual information based on the evidence that the integration between more sensory modalities enables to improve the accuracy of the qualitative assessment [6]. The role played by the force feedback for hard masses identification was evaluated by comparing localization accuracies in visual-only mode and visuo-haptic mode. In addition, qualitative evaluation of the developed simulator by a group of urologists was carried out.

2 Background and Related Works

2.1 Magnetic Resonance Elastography

Elastography is a non-invasive imaging technique that provides quantitative information about the mechanical properties of soft tissues, usually assessed by manual palpation. Magnetic Resonance Elastography is an elastographic technique that assesses the shear modulus (i.e., stiffness) of tissues by analyzing the propagation of mechanical waves. Several studies have confirmed that prostate cancer is characterized by a significant increase in stiffness if compared to the surrounding soft tissues, due to some irreversible morphological changes [7], thus suggesting that tissue elasticity is an excellent biomarker for PCa detection [8]. MRE offers the potential to provide accurate information about both the location and the size of prostate tumors, regardless of their dimensions, in a non-invasive way. The 3D elastograms (i.e., maps of tissue stiffness distribution) give information about the whole 3D region of interest, overcoming the limitations of conventional 2D imaging techniques, and can be reproduced on a computer screen by means of one of the existing computer graphics rendering methods.

2.2 Haptics-Based Virtual Reality Systems for Prostate Cancer Diagnosis

Some haptics-based virtual reality (VR) systems whose goal is to improve prostate cancer diagnoses have been already proposed. However, the aim of all the systems found in literature is to simulate real diagnostic procedures for training purposes, and not to provide an alternative diagnostic tool. The main haptics-based simulators found in this field deal with digital rectal examinations (i.e., the manual palpation of the gland from the rectum), being the tactile component the main character of the actual procedure. DRE simulators allow trainees to familiarize with this examination, which is quite challenging to learn due to the fact that it is difficult to find patients volunteering as practice subjects as well as it is problematic for an expert urologist to give a feedback on the trainee performance about a procedure that relies only on tactile feedback. DRE simulators are usually mannequin-based, but some employing virtual reality exist, like the one proposed by Burdea et al. in which a PHANToM haptic interface provides forces back to the user's finger after he/she interacts with one of the four virtual prostate models available [9]. Anyway, this simulator lacks of a realistic haptic feedback and allows to train the procedure with a limited number of pathological cases. A more recent simulator for the same procedure has been proposed by the Imperial College of London and it is called robotic "trainer rectum". The technology consists of a silicone rectum where the doctor inserts his finger and feels the exact sensations of the procedure thanks to some robotic arms able to apply pressure. While performing the task, the physician can use 3D glasses to see a full three-dimensional model of the rectum and the prostate on a computer screen. Although the trainee has at his disposal several anatomies to train with, a patient-specific scenario is not achieved [10].

2.3 Haptic Elastography

The fact that elastograms provide quantitative information about tissue stiffness, a material property usually experienced with the sense of touch, enables to consider MRE as a valuable tool for haptic feedback modeling. Anyway, since it is a quite innovative imaging technique not so many publications conjugating MRE and haptics can be found in the literature, and even fewer dealing with prostate cancer.

SenseViewer is an interface able to render multiple cues (visual, auditory and haptic) in medical images, implemented by Li et al. [11]. Stiffness and damping parameters employed to produce the haptic feedback of the images are derived from MRE values. This interface however requires the user to design some rendering models by himself and has not been extended to 3D case yet. Combination between haptic technology and elastography was proposed by Suzuki et al. [12] as well. The main achievement of this approach is that the provided haptics rendering accounts for the whole three-dimensional elasticity distribution, obtained with ultrasounds. This means that the computation of the reaction force does not only depend on the pressing position, but also on the depth of hard masses and on the ambient elasticity around the pressure point. Anyway, the implemented feedback requires a series of parameters which are estimated in this work from artificial biological bodies fabricated with reference to the elasticity of breast tissue, and not of the prostate. The most recent work in this field is the one presented by Zumba [13]. He implemented two different approaches to combine MRE data with haptic cues. In the first one, the haptic effect combined a proxy-based surface haptic method with a volume haptic algorithm where the spring-like force depended on the punctual value of stiffness obtained from MRE. The main drawback of this implementation is that sharp transitions in the punctual elasticity values led to vibrations and buzzing of the device. A more stable haptic rendering was obtained with the second approach. Three isosurfaces were defined by individual ranges of voxel intensities and different haptic properties were given to them. Since in this case the feedback relied only on volumetric data, there was no necessity to create polygonal meshes. Anyway, this algorithm can deliver just three main force feedback, preventing the user from finely discriminate among different stiffness regions.

3 Materials and Methods

3.1 System Overview

The developed visuo-haptic simulation runs on a Windows platform where the graphic and the haptic threads run concurrently, but at different speeds (graphic frames and haptic frames are rendered at 60 Hz and 1000 Hz respectively). It was implemented exploiting the functionalities of *LACE library*, a C++ based platform that provides an intuitive environment for the development of medical applications, which relies on Visualization Library [14] to obtain high-performance 3D graphics and QuickHaptics^{TM} for real-time haptics rendering [15]. The basic elements that interact in the simulation are shown in Figure 1.

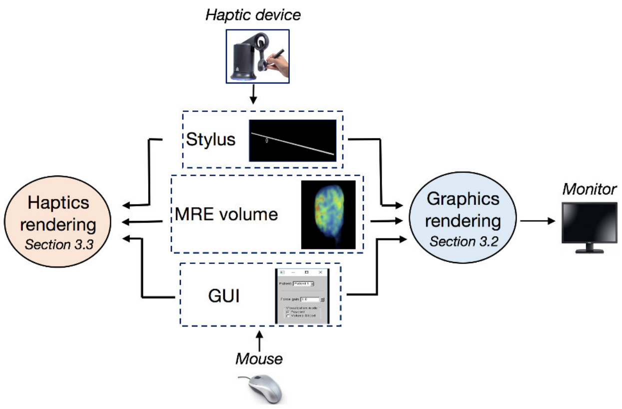


Fig. 1 Basic elements of the application. The graphic scene is populated by the haptic cursor, a white stylus following in real-time the movements of the haptic device, the MRE prostate volume, and the graphic user interface (GUI). The haptics rendering reads the haptic device status, compares its position with the volume, and provides force feedback to the user. Volume rendering properties and force parameters can be interactively set through the GUI.

3.2 Graphics Rendering

MRE volume is rendered with the raycasting technique, which enables to view the internal parts of the volume (Figure 2). A custom-made transfer function and a default opacity level were defined, in such a way that hard masses appear with a red color while soft parts are blue. Anyway, the user can fine tune transfer function parameters through the GUI, to obtain the most appropriate view for volume exploration. In order to provide a spatial reference, the volume is visualized within its bounding box, where some texts enable to keep track of the relative position of prostate apex, base, and its left and right sides. The graphic cursor follows in real-time the movements of the haptic stylus. It is rendered in the scene as a cylindrical shape with a red tip, to allow a more intuitive understanding of the position of the interacting point with respect to the volume. An additional feature is that the volume can be dragged in the scene according to cursor movements, by pressing the first button of the haptic device. In this way it is possible for the user to explore the anatomy both visually and haptically from different perspectives. It is important to highlight that the volumes used

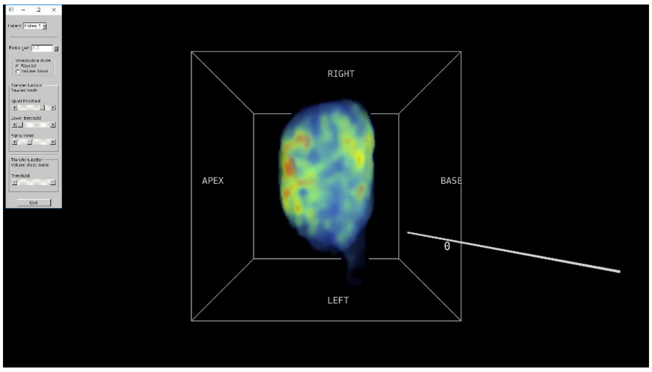


Fig. 2 Starting configuration of the application. The elements that can be appreciated are: the volume, rendered with the raycast mode, with its bounding box, the haptic cursor and the graphic user interface.

in the application represent just the real part $Re(\omega)$ of the complex shear modulus $G(\omega)$[1], which embodies the main information about stiffness. Image processing was performed to improve both graphic and haptic performances, by reducing the computational load. In particular, a median filter with a window of 5 voxels was applied to smooth the original images, and data were converted into eight bit unsigned int, thus leading to stiffness ranging between 0 and 255 (as described in detail in [13]).

3.3 Haptics Rendering

Haptic cues were added to the simulation to support and strengthen the visual cues, enhancing the surgeon experience during prostate exploration. In fact, several studies have confirmed that visuo-haptic integration is very useful, especially when it is necessary to spatially locate some specific features within a volume [16]. It is important to highlight that the rendered forces do not represent a realistic simulation of the tactile feedback the user would receive if interacting with internal prostate tissues. Rather, they are just aimed to exaggerate the tactile feedback obtained with real prostates, enhancing the user experience while exploring the data, making it possible to easily detect tumor masses within the volume. The haptic algorithm implemented here belongs to the category of volume haptics algorithms. The delivered force feedback depends just on the volumetric dataset (in our case MRE data), thus eliminating the need of pre-processing steps required for surface representation. The main feature of the implemented volume force is that both the local stiffness at the cursor tip and the one of the surrounding voxels have been considered. Both these contributions have been

[1] $G(\omega) = Re(\omega) + jIm(\omega)$, where ω represents the stimulation frequency.

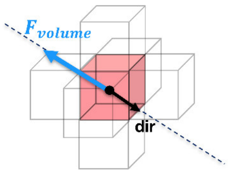


Fig. 3 $\mathbf{F_{volume}}$ direction. The device is moving on the dashed line from top to bottom, resulting in direction **dir** shown as a black vector. The current contact point, represented as a black dot, is within the voxel highlighted in red. Resulting $\mathbf{F_{volume}}$ is shown in blue. Not-colored voxels are those considered for gradient computation ((3)).

taken into consideration since it is of common knowledge that the feedback perceived when touching a real object does not depend only on the hardness of the contact point, but also on the stiffness of its surroundings, so both are needed to obtain a complete representation of volume data by force sensation.

The magnitude of the elasticity-dependent force ($\mathbf{F_{volume}}$) is given by the sum of a part ($F_{punctual}$) which is linearly dependent on the local elasticity (i.e., the MRE value at the cursor tip $\mathbf{x_{tip}}$) and another ($F_{surrounding}$) that depends on the directional derivative of the volume data at that point (which corresponds to $\mathbf{x_{tip}}$ again), weighted by a gain k that can be set by the user through the GUI. Default gain value (k) is set to 1 and it has an upper limit of 3 (corresponding to the value which prevents the device from exceeding the maximal force it is capable of). The force $\mathbf{F_{volume}}$ is in the opposite direction with respect to **dir**, a normalized vector pointing in the direction in which the device is moving, computed as difference between haptic device positions at current and previous haptic frames ($\mathbf{dir}(t) = \mathbf{x_{tip}}(t) - \mathbf{x_{tip}}(t-1)$, with t = current frame) (Figure 3) (1).

$$\mathbf{F_{volume}}(\mathbf{x_{tip}},t) = -k(F_{punctual}(\mathbf{x_{tip}},t) + F_{surrounding}(\mathbf{x_{tip}},t))\mathbf{dir}(t) \quad (1)$$

The scalar term representing punctual stiffness contribution $F_{punctual}$ varies between 0 and 1 with linear trend. It allows to provide a feedback that is correlated to the relative hardness of the exact point at which the device is found in the current haptic frame, and it is computed as the ratio between the MRE value[2]at the cursor tip ($MRE(\mathbf{x_{tip}},t)$) and the maximum MRE value (computed as the greatest value found in the considered elastogram):

$$F_{punctual}(\mathbf{x_{tip}},t) = \frac{MRE(\mathbf{x_{tip}},t)}{\max\limits_{1 \le i \le N} MRE(i)} \quad (2)$$

where i is the voxel number, and N is the total number of voxels. The second term $F_{surrounding}$ takes into account the effect of the neighboring voxels, through data gradient. Mapping the gradient of scalar values to a force is a very common approach in volume haptics [17]. In our case, the gradient at the device position is not directly mapped to the force, but it is used to calculate the directional derivative at that point. The directional derivative allows one to determine how the scalar field (i.e., MRE values) changes in a particular direction. It is computed by taking the dot product between the gradient in x, y, z coordinates $\nabla(MRE(\mathbf{x_{tip}},t))$, computed with the central differences method, and the vector pointing in the selected direction **dir**. As a consequence, this contribution to the force is proportional to the extent at

[2] MRE value at a generic point **x** corresponds to the real part of the shear modulus of the voxel associated to the position **x**.

which voxel values are changing at the current position, in the direction of motion.

$$F_{surrounding}(\mathbf{x_{tip}},t) = \nabla(MRE(\mathbf{x_{tip}},t)) \cdot \mathbf{dir}(t) \tag{3}$$

The gradient is computed only once at the beginning and stored in memory, to avoid delays during the haptic rendering process. The final force provided to the user does not consist just of the volume force, but some constant contributions are added to enhance the difference in tactile feedback between very different sets of stiffness, as expressed in (4).

$$\mathbf{F_{total}}(\mathbf{x_{tip}},t) = \mathbf{F_{volume}}(\mathbf{x_{tip}},t) + \mathbf{F_{friction}}(t) + \mathbf{F_{damping}}(t) + \mathbf{F_{gravity}} \tag{4}$$

Values assigned to these further contributions are intrinsically normalized to 1 by Quick Haptics^{TM} (this means that if we assign a value of 1, the library will interpret it as the maximal value for that contribution the device is capable of rendering). First, either a low or high friction contribution $\mathbf{F_{friction}}$ is added depending on the relationship between local elasticity and a threshold set to a percentage of the maximal stiffness value of the elastography data, in the device direction of motion. In our case, this threshold was fixed to the 55% of the maximal value, empirically determined (5).

$$\begin{aligned} &\mathbf{F_{friction}}(t) = 0.2\mathbf{dir}(t) \quad \text{if} \quad MRE(\mathbf{x_{tip}},t) < 0.55 \max_{1 \le i \le N} MRE(i) \\ &\mathbf{F_{friction}}(t) = 0.6\mathbf{dir}(t) \quad \text{otherwise} \end{aligned} \tag{5}$$

The second contribution consists of a damping force $\mathbf{F_{damping}}$ always in direction **dir**, whose gain is set to the default value of 0.3 (6). This value has been established empirically as the one able to guarantee a perfect trade-off between instability minimization and natural feedback delivery.

$$\mathbf{F_{damping}}(t) = 0.3\mathbf{dir}(t) \tag{6}$$

However, when the tip of the device is found in an area where the punctual stiffness is very high (i.e., greater than the same percentage threshold defined for the friction) for some time (in our case, more than 10 consecutive haptic frames), the damping is set to its maximal value, as reported in (7). If we are in this situation, it means that the cursor is in a very hard region and therefore the user should experience high resistance when trying to penetrate this section of the prostate tissue.

$$\begin{aligned} &\mathbf{F_{damping}}(t) = 1.0\mathbf{dir}(t) \\ &\text{if} \quad MRE(\mathbf{x_{tip}},t) \ge 0.55 \max_{1 \le i \le N} MRE(i) \quad \text{for} \quad t-10,...,t \end{aligned} \tag{7}$$

Moreover, a compensation for the weight of the haptic device stylus has been added through $\mathbf{F_{gravity}}$ in vertical direction **j**, empirically established (8).

$$\mathbf{F_{gravity}} = 0.1\mathbf{j} \tag{8}$$

At this point, the magnitude of the computed force is averaged with the magnitudes of the forces provided in the 5 previous frames, to enable smoother transitions between consecutive forces (9). This step was added since a common problem of volume haptics algorithms is that when the device is moving fast, it can encounter huge and sudden stiffness changes that cause unstable feedback and haptic device vibrations [18].

$$|\mathbf{F_{total}}(t)| = \frac{1}{6}\sum_{t-5}^{t}(|\mathbf{F_{total}}(t)|) \tag{9}$$

As a final step, a check on the final force magnitude is performed, to prevent the device from trying to render forces that exceed its physical limits (i.e., 3.4N).

4 Experimental Evaluation and Results

Two different kinds of experiments were conducted. The first one aimed to evaluate the role of the tactile feedback in helping for an accurate detection of hard masses, with respect to visualization of prostate's stiffness map alone. To this purpose, we compared users' performances in finding and localizing hard masses without and with force feedback. The second evaluation we performed consisted in a qualitative evaluation of the simulator by expert urologists, who were asked to fill some questionnaires. The purpose of this investigation is to better understand if using visual and haptic simulation of prostate helps to improve surgeons' ability to perform prostate biopsy and prostatectomy.

4.1 Haptic Feedback Evaluation and Results

The evaluation phase was performed at Politecnico di Milano (Italy), where the available setup includes a NVIDIA TITAN Xp graphics card and a a 3D Systems Touch (formerly Sensable Phantom Omni) haptic device [15] Figure 4. The experiment involved 15 biomed-

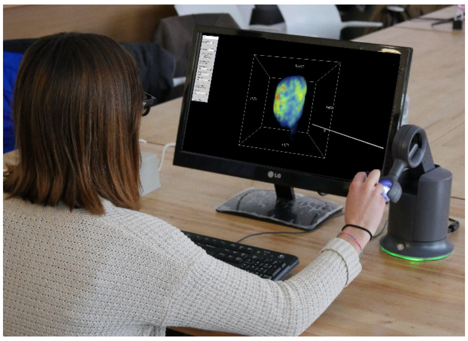


Fig. 4 A participant while testing the application, with the setup available at Politecnico di Milano. The monitor is rendering the MRE volume and the graphic cursor, whose movements are mapped to those of the 3D Systems Touch haptic device (which can be seen on the right).

ical engineers (average age of 27) with minor or no previous experience with the simulator. The task consisted in exploring prostate anatomy firstly without and secondly with haptic feedback and localizing hard regions. Users were asked to:

1. Interact with the volume, dragging it in the scene;
2. Place the cursor inside a hard region;
3. Press a key when they think they are inside a hard region, to save the position;
4. Repeat the process until they think they have found all the major hard spots (visual);
5. Repeat the same procedure with the addition of haptic feedback (visuo-haptic).

No time limit was imposed, thus the users were set free to interact with the volumes as much as they liked, and they were not told how many hard areas they were supposed to find. However, the amounts of time spent for visuo and visuo-haptic interactions were saved for statistical analyses. The MRE dataset available for the testing phase comes from excised prostates of patients who underwent radical prostatectomy at University of Illinois at Chicago (UIC) hospital. Specimens were scanned with a modified 9.4T ultra-high field pre-clinical scanner, employing the phase constant SLIM-MRE method [19]. The complete description of MRE acquisition constituted an experiment on its own and can be found in [20]. Each participant was asked to repeat the task for two prostates. The former patient is a subject characterized by multi-focal cancer (i.e., he has more than one lesion, concentrated in the same region), while the latter has just a couple of significant lesions.

Two different parameters were computed to assess localization accuracy. First of all, a percentage accuracy $ACC_{\%}$ is calculated to evaluate how many times the subject was able to correctly place the haptic cursor in a position corresponding to a ”hard” voxel among all the times he/she believed to be inside one. $ACC_{\%}$ is defined as ratio between the number of high stiffness voxels (i.e., positions) correctly identified by the user N_{hard} and the total number of positions selected by the same user N_{tot}, as expressed in (10). Hard voxels were defined as those associated to a value overcoming the same threshold we selected for hard masses definition in haptic feedback implementation.

$$ACC_{\%} = \frac{N_{hard}}{N_{tot}} \tag{10}$$

The obtained values for visual and visuo-haptic mode were then compared to evaluate statistical difference, using the left-tailed sign test at 5% significance level. Obtained results are shown in Figure 5. A statistically significant difference in median percentage accuracies

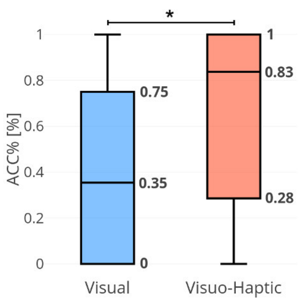
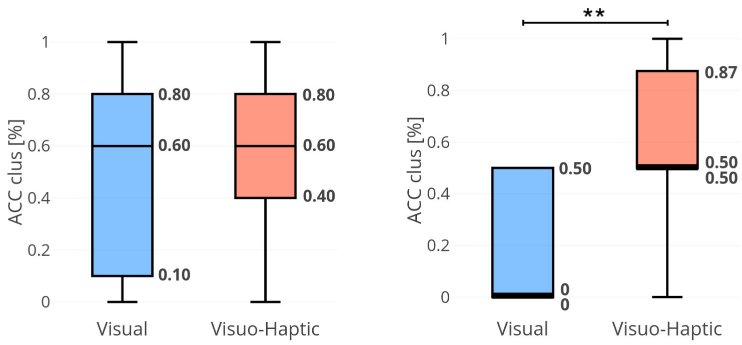


Fig. 5 Percentage accuracy $ACC_{\%}$ for visual and visuo-haptic exploration (sign test, ($pvalue < 0.05$)).

$ACC_{\%}$ between visual and visuo-haptic modalities can be observed. The median value of $ACC_{\%}$ for visuo-haptic exploration exceeds the double of the value obtained for visual one.

The second parameter we computed for accuracy evaluation ACC_{clus} is defined as percentage of high stiffness areas identified by the subject on the total number of hard masses. It allows to understand if the participants were able to target all the main hard masses that could be found in each anatomy. To achieve this, the number of the main high stiffness areas for both the patients was determined by a clustering procedure, resulting in a total of 5 and 2 main high stiffness areas assigned to patient 1 and 2 respectively. After testing by the users, we considered the coordinates of the high stiffness regions each of them localized, and we looked for the cluster each coordinate belonged to. Afterwards, we computed the total number of clusters they were able to identify N_{target} (i.e., the number of clusters for which they were able to target at least one point belonging to it) and we evaluated accuracy ACC_{clus} according to the following formula:

$$ACC_{clus} = \frac{N_{target}}{N_{clus}} \tag{11}$$



(a) Patient 1 (sign test, ($pvalue > 0.05$)). (b) Patient 2 (sign test, ($pvalue < 0.05$)).

Fig. 6 Accuracy ACC_{clus} computed as percentage of identified clusters in visuo and visuo-haptic modalities.

where N_{clus} represents the total number of significant clusters for each anatomy ($N_{clus} = 5$ for patient 1, $N_{clus} = 2$ for patient 2). The boxplots in Figure 6 show the main results for ACC_{clus}. The anatomies were kept separated since the number of masses was different in each of them. If we consider the results obtained for patient 1, it is possible to notice that the median value does not change when comparing the two modalities. However, it is possible to infer that the average number of detected masses is greater in visuo-haptic mode. Thus, users were able to detect more lesions among the 5 main regions identified for patient 1, on average, but the difference is not significant. The same does not apply for patient 2, for which our results show the existence of a significant improvement between the two modalities (sign test, at 5% significance level).

Finally, we considered the ratio between the percentage accuracy (defined as $ACC_{\%}$ in (10)) and the percentage time spent in each mode, as reported in the following equation:

$$AT = \frac{ACC_{\%}}{t_{\%}} \tag{12}$$

where $t_{\%}$ is defined as the ratio between the time spent by the user in each modality (visual or visuo-haptic) and the total time. This parameter allows to assess the relationship between accuracy and the time spent for the exploration in the two modalities. The *accuracy in time AT* ratio increases with increasing accuracy and decreasing time. The most desirable situation is to achieve high accuracy in a small amount of time. After normalizing the ratio between 0 and 1, we compared the accuracy obtained with respect to time in the two situations. Results obtained for the *accuracy in time AT* ratio when both the anatomies are considered together are shown in Figure 7. A relevant increase in the value of this parameter between visual and visuo-haptic modality can be observed. In particular, the median value of this ratio passes from 0.20 to 0.53, and the difference is statistically significant at 5% significance level.

4.2 Qualitative Evaluation and Results

To perform a qualitative evaluation of the developed simulator by its potential final users, we recruited 8 experienced urologists from institutions collaborating with either Politecnico di Milano or Mixed Reality Lab. Two of them were from Ospedale Maggiore Policlinico,

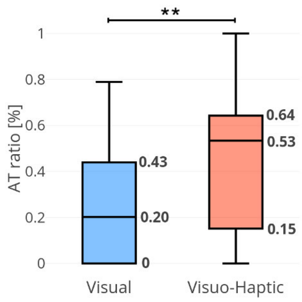


Fig. 7 Accuracy in time *AT* ratio for visual and visuo-haptic exploration (sign test, ($pvalue < 0.05$)).

one from Ospedale Niguarda, one from Istituto Europeo di Oncologia and four from UIC Hospital. Urologists were asked to:

1. Look at the MRE reconstruction of the prostate containing cancer on the computer;
2. Interact with the anatomy through the haptic device, to virtually feel how stiff the tissue is in different parts;
3. Complete a questionnaire about their experience;
4. Complete a second questionnaire about the usability of the simulator (just for Italian urologists).

The questionnaire for the qualitative assessment of the simulator consisted of 12 questions: some of them were general (1-7) and others were specifically targeted at collecting urologists' feedback about their experience with the simulator (8-12). Users could choose among five possible answers, to indicate the extent of agreement or disagreement to each question (1: Not at all, 2: Somewhat, 3: Fairly, 4: Very, 5: Extremely). Figure 8 reports questions and answers from 8 to 12, being them the most relevant for this study.

The four Italian urologists and one general surgeon were asked to fill a second questionnaire, called System Usability Scale (SUS). SUS is a simple ten-item scale developed by Brooke et al. [21] which allows to subjectively assess new technology usability. The respondent has to indicate his/her extent of agreement or disagreement to each statement on a 5 point scale (from 1 -Strongly Disagree- to 5 -Strongly Agree-). SUS score is a single number in the range 0-100 that represents a measure of the overall usability of the system being evaluated. Results of the SUS evaluation are reported in Table 1. The mean SUS score obtained was 55.00 ± 3.95 (range: 0-100).

5 Discussion

In this thesis, we developed an application where patient-specific 3D model of the prostate is graphically rendered exploiting volume rendering techniques. Visual information was complemented with a force feedback that relies on the true viscoelastic properties of the gland, to improve localization accuracy. By accounting for both the punctual value of stiffness and the elasticity of the surrounding regions, the provided force enables to easily perceive the difference in hardness between healthy and unhealthy tissue. Thanks to these features, the developed algorithm provides a smooth and stable force, and successfully overcomes the main limitations of the other approaches proposed in the literature for haptic cues implementation from elastographic data.

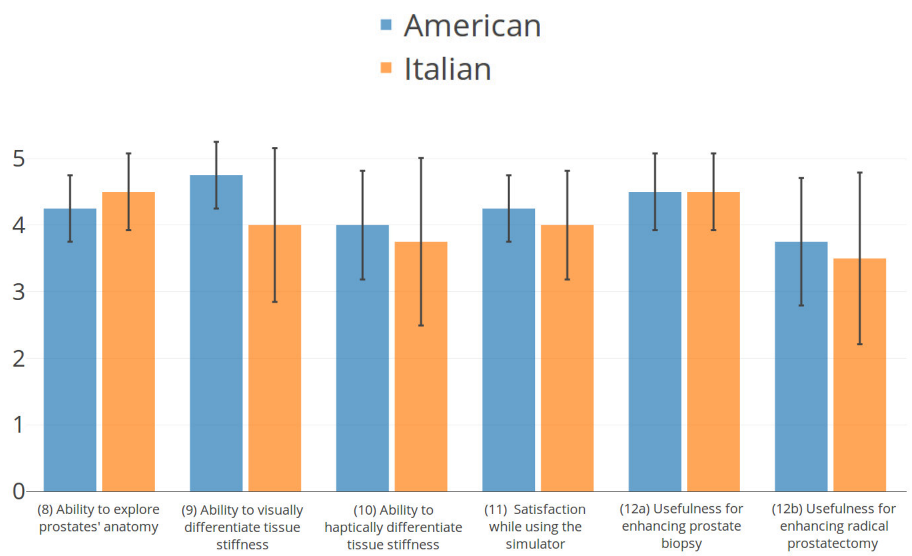


Fig. 8 Average results of the questionnaire to questions from 8 to 12. The vertical bar represents the standard deviation. Scores by American (blue) and Italian (orange) urologists are kept separate.

Table 1 Results of the System Usability Scale evaluation.

N	Statement	Mean±Std Dev
1	I think that I would like to use this system frequently.	3.6±0.9
2	I found the system unnecessarily complex.	1.2±0.4
3	I felt very confident using the system.	3.6±0.9
4	I found the various functions in this system were well integrated.	4.2±0.8
5	I thought the system was easy to use.	4.0±0.7
6	I thought there was too much inconsistency in this system.	1.4±0.5
7	I found the system very cumbersome to use.	1.2±0.4
8	I would imagine that most people would learn to use this system very quickly.	4.2±0.4
9	I think that I would need the support of a technical person to be able to use this system.	2.2±1.6
10	I needed to learn a lot of things before I could get going with this system.	1.4±0.5

We conducted some experiments to evaluate the role played by the haptic feedback in the improvement of the visual exploration of the anatomy. Results obtained for the percentage accuracy $ACC_{\%}$ reveal that the users were more likely to correctly target a high stiffness region when supported by the haptic cues. Since this kind of accuracy accounts for the number of times each user was able to correctly select a hard mass, and not for the number of major hard masses identified, we also evaluated accuracy as percentage of main high-stiffness areas each participant was able to recognize with ACC_{clus}. The results we obtained for this measure are slightly different for the two considered anatomies. This is probably due to the different distribution of hard regions within the volumes: while in the first case the 5 masses were wider and so it was easier to correctly target them also without any tactile cues, in the second case the 2 lesions were smaller, making more challenging the placing of the cursor within both of them without any haptic help. Evaluating both $ACC_{\%}$ and ACC_{clus}, we can conclude that haptic feedback seems to be of help to increase the accuracy, since it decreases the error rate in hard masses selection ($ACC_{\%}$) and improves the average number of areas identified (ACC_{clus}). An exhaustive evaluation with further anatomies needs to be carried out, especially for ACC_{clus} estimate. As our data suggest, this type of accuracy is highly dependent on the patient's clinical situation, therefore its values may change considerably according to the considered anatomy. We eventually investigated if the addition of haptic feedback is able to improve the accuracy and lower the time needed for exploration at the same time, with the *accuracy in time AT* ratio. The improvement of the *AT* ratio shown by our data allows us to conclude that when forces are present, they help to target stiff areas more accurately in a smaller amount of time. Therefore, haptic cues are able to easily drive the user towards hard masses, letting him/her save time needed for volumetric exploration, and fix the haptic cursor inside the masses as well, increasing the overall detection accuracy. Experimental outcomes demonstrate that the implemented haptic feedback plays a role in facilitating the process of targeting hard masses. Since it does not rely on prostate-specific parameters, it has promising prospects for being applied to other procedures where it is important to precisely reach damaged areas, even outside the urological field. Further anatomies will be included in future experiments to achieve a more complete evaluation. Moreover, a group of expert urologists needs to be recruited to verify coherence of the results with those obtained by the population of students available for this study, and to assess a possible introduction in the clinical practice.

The simulator has also been qualitatively evaluated by a cohort of 8 expert urologists, recruited from both American and Italian institutions. When considering the questions more strictly related to the simulator, we can notice that there are not considerable differences between the two groups. The average score for questions 8 to 12 is always higher than 3, revealing an overall satisfaction in anatomy exploration using the simulator by both the groups. The last evaluation we performed, with the System Usability Scale, allows us to get just a preliminary impression about the general usability of the simulator since our sample is too small. The mean SUS score we obtained is of 55 out of 100. According to the study carried out by Bangor et al. in [22], the system has an overall "Good" usability. However, even if the result seems already promising, a wider population must be recruited in order to draw exhaustive conclusions.

Differently from existing VR-based applications dealing with PCa diagnostic process, the proposed methodology does not aim at training a diagnostic procedure, but rather at becoming an alternative or a complementary tool for the diagnosis itself. Future work would therefore involve the comparison with current diagnostic procedures, like PSA, DRE, and histological reports, to establish the diagnostic accuracy of the developed application, following some already proposed approaches [23]. This will especially imply an extensive research in the MRE field, to further assess the role of this imaging technique for PCa detection. Indeed, the main potentiality, but at the same time the main limitation, of this approach relies on MRE technology. Although MRE has demonstrated to provide promising results for PCa detection, the procedure still presents some major challenges. Above all, at the moment it has been applied mainly to ex-vivo prostates, due to the fact that it is difficult to induce adequate shear waves in a patient-friendly manner and the signal to noise ratio in acquisitions made with conventional clinical scanners at 1.5T is too high [8]. Applying the technique to in-vivo cases despite these limitations will lead to acquisitions unable to resolve small stiff areas which are likely to correspond to cancer. Therefore, clinical application in the pre-operative reality is difficult to be imagined nowadays, but some first acquisitions of in-vivo anatomies were performed and showed promising results [24] [25].

6 Conclusions

The achieved simulation of prostate cancer has the advantage of integrating both visual and tactile information on a patient-specific 3D model of the prostate obtained from MRE. The experimental results indicate that the integration of visual information with haptic feedback is able to enhance the surgeon experience during prostate exploration, and enables to spatially locate hard masses within the volume with increased accuracy and in a smaller amount of time with respect to visualization only. Therefore, the proposed system has the potential to allow for a more accurate biopsy targeting as well as an improvement in pre-surgical planning phase.

References

1. World Health Organization (2012) Prostate cancer: Incidence, mortality and prevalence in 2012. `http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx`
2. Harvard Medical School (2017) Prostate knowledge. `https://www.harvardprostateknowledge.org/category/prostate-cancer`
3. de Rooij M, Hamoen EH, Fütterer JJ, Barentsz JO, Rovers MM (2014) Accuracy of multiparametric mri for prostate cancer detection: a meta-analysis. American Journal of Roentgenology 202(2):343–351
4. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay D (2013) How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Canadian Urological Association Journal 7(5-6):293–8
5. Grossfeld GD, Latini DM, Lubeck DP, Mehta SS, Carroll PR (2003) Predicting recurrence after radical prostatectomy for patients with high risk prostate cancer. The Journal of urology 169(1):157–163
6. Ernst MO, Bülthoff HH (2004) Merging the senses into a robust percept. Trends in cognitive sciences 8(4):162–169
7. Krouskop TA, Wheeler TM, Kallel F, Garra BS, Hall T (1998) Elastic moduli of breast and prostate tissues under compression. Ultrasonic imaging 20(4):260–274
8. Good DW, Stewart GD, Hammer S, Scanlan P, Shu W, Phipps S, Reuben R, McNeill AS (2014) Elasticity as a biomarker for prostate cancer: a systematic review. BJU international 113(4):523–534
9. Burdea G, Patounakis G, Popescu V, Weiss RE (1999) Virtual reality-based training for the diagnosis of prostate cancer. IEEE Transactions on Biomedical Engineering 46(10):1253–1260
10. Imperial College of London (2016) Robotic rectum may aid prostate cancer diagnosis. `http://www3.imperial.ac.uk/newsandeventspggrp/imperialcollege/newssummary/news_4-7-2016-13-54-15`
11. Li BN, Shan X, Qin J, Huang W, An N (2013) Senseviewer: A unified rendering interface of visual and haptic cues in medical images. In: Robotics and Biomimetics (ROBIO), 2013 IEEE International Conference on, IEEE, pp 2209–2212
12. Suzuki S, Hamamoto K (2016) Haptic rendering for a virtual palpation system. Electronics and Communications in Japan 99(5):27–36
13. Zumba D (2016) Haptic simulation of prostate cancer based on magnetic resonance elastography. Master's thesis, University of Illinois at Chicago
14. Bosi M (2016) Visualization Library. `http://visualizationlibrary.org/docs/2.0/html/index.html.`, accessed: 30 October 2017

15. 3D Systems, Inc (2016) Touch Haptic 3D Stylus. `http://www.geomagic.com/en/products/sculpt/touch/`, accessed: 30 October 2017
16. Avila RS, Sobierajski LM (1996) A haptic interaction method for volume visualization. In: Visualization'96. Proceedings., IEEE, pp 197–204
17. Iwata H, Noma H (1993) Volume haptization. In: Virtual Reality, 1993. Proceedings., IEEE 1993 Symposium on Research Frontiers in, IEEE, pp 16–23
18. Kim SY, Ryu JH, Lee W (2015) Palpation simulator with stable haptic feedback. Minimally Invasive Therapy & Allied Technologies 24(4):211–217
19. Klatt D, Yasar TK (2013) Sample interval modulation magnetic resonance elastography. US Patent App. 14/648,081
20. Kearny S (2016) Advances in elastography using geometrically focused actuation. PhD thesis, University of Illinois at Chicago
21. Brooke Jea (1996) Sus-a quick and dirty usability scale. Usability evaluation in industry 189(194):4–7
22. Bangor A, Kortum P, Miller J (2009) Determining what individual sus scores mean: Adding an adjective rating scale. Journal of usability studies 4(3):114–123
23. Sahebjavaher RS, Nir G, Gagnon LO, Ischia J, Jones EC, Chang SD, Yung A, Honarvar M, Fazli L, Goldenberg SL, et al (2015) Mr elastography and diffusion-weighted imaging of ex vivo prostate cancer: quantitative comparison to histopathology. NMR in Biomedicine 28(1):89–100
24. Pepin KM, Ehman RL, McGee KP (2015) Magnetic resonance elastography (mre) in cancer: Technique, analysis, and applications. Progress in nuclear magnetic resonance spectroscopy 90:32–48
25. Arani A, Plewes D, Krieger A, Chopra R (2011) The feasibility of endorectal mr elastography for prostate cancer localization. Magnetic resonance in medicine 66(6):1649–1657