MRI/TRUS data fusion

Prostate cancer diagnostic and focal treatment.

David Manuel Galaz Tavares
(BSc)

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Jury
Chairman: Professor Ana Teresa Correia de Freitas
Advisor: Professor Jorge Manuel Mateus Martins
Members: Professor João Miguel Raposo Sanches
           Doctor Arlindo Jorge de Abreu Fonseca
           Doctor Jorge Manuel Trindade Rebola

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Scientists discover the world that exists; engineers create the world that never was.

Theodore Von Karman
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Abstract

Prostate cancer is the most common non-skin cancer in men and with a tendency to increase as the world population ages. Currently, there is no image modality that can both provide accurate needle navigation and be cost-effective, therefore limiting the ability to perform targeted biopsies and/or focal therapy. Thus multi-modality registration of both MRI and TRUS images has been the most consensual solution. Following this line of research, in this work, a method combining semi-automatic segmentation followed by elastic registration is developed for the brachytherapy procedure. The semi-automatic segmentation is based on Active Shape Models (ASM), and the non rigid registration technique to pre-interventional MRI is based on Thin-Plate Splines interpolation. Using the developed tools for brachytherapy, a study is also performed for the biopsy procedure. This study quantifies the movement of the prostate gland during the biopsy procedure due to external loads from the contact of the tip of the ultrasound probe.

Keywords

Prostate cancer, Semi-automatic segmentation, Active Shape Models(ASM), MRI/TRUS image Registration, Thin-Plate Splines
Resumo

O cancro da próstata é o mais comum entre homens e com tendência para aumentar com o envelhecimento da população mundial. Actualmente, nenhuma técnica imagiológica consegue ao mesmo tempo proporcionar uma navegação de agulhas precisa e ser rentável, dificultando por isso a capacidade de executar biópsias direcionadas e/ou terapias focais. Assim, o registo de imagens entre MRI e TRUS tem sido a solução mais consensual. Seguindo essa linha de investigação, neste trabalho foi desenvolvido um método que combina segmentação semiautomática seguida de um registo elástico, para ser aplicada à braquiterapia da próstata. A segmentação semiautomática é realizada com base em *Active Shape Models (ASM)*, enquanto a técnica de registo não rígido em MRI pré-intervencional é baseada em interpolação por *Thin-Plate Splines*. Utilizando os métodos desenvolvidos para a braquiterapia, foi também realizado um estudo para o caso das biópsias. Este estudo quantificou o movimento da próstata durante o procedimento da biópsia sob a acção de forças exteriores induzidas pelo contacto com a sonda de ultra-sonografia transrectal.

Palavras Chave

Cancro da próstata, Segmentação semi-automática, *Active Shape Models (ASM)*, Registo de imagem MRI/TRUS, *Thin-Plate Splines*
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Abbreviations

**ADC**  Apparent Diffusion Coefficient
**AS**  Active Surveillance
**ASM**  Active Shape Models
**CT**  Computed Tomography
**DCE**  Dynamic Contrast Enhanced
**DSC**  dice similarity coefficient
**DRE**  Digital Rectal Examination
**DWI**  Diffusion Weighted Imaging
**FEA**  Finite Elements Analysis
**ICP**  Iterative Closest Point
**MAD**  mean absolute distance
**MRI**  Magnetic Resonance Imaging
**MRS**  Magnetic Resonance Spectroscopy
**PCa**  Prostate Cancer
**PCA**  principal components analysis
**PSA**  Prostate Specific Antigen
**P2P**  point to point
**P2S**  point to surface
**RBF**  Radial Basis Functions
**RP**  Radical Prostatectomy
**ROI**  region of interest
**SSM**  Statistical Shape Model
TRUS Transrectal Ultrasound

TPS Thin-Plate Splines

SNR signal to noise ratio
List of Symbols

In the remaining of this work, the following notation is used:

\( a \) for scalar values
\( a \) for vectors
\( A \) for matrices

The symbols used in this work are listed below:

\( A \) matrix that represents the affine transformation
\( b \) parameter vector in terms of eigenmodes
\( c \) polynomial coefficients vector
\( C \) covariance matrix of the vector shapes
\( D \) diagonal eigenvalues matrix
\( I \) identity matrix
\( P \) points matrix padded with zeros for the RBF computation
\( Q \) partial eigenvectors matrix
\( Q_{1} \) product of QR decomposition
\( Q_{2} \) product of QR decomposition
\( r \) partial observations vector
\( R \) rotation matrix
\( R_{1} \) product of QR decomposition
\( s \) shape vector
\( \bar{s} \) mean shape vector
\( U \) eigenshapes matrix
\( W \) matrix that describes the warping transformation
\( \alpha \) weight that controls continuity energy in ASM
\( \beta \) weight that controls curvature energy in ASM
\( \gamma \) weight that controls shape energy in ASM
\( \phi \) radial basis function
\( \Phi \) radial function matrix
Introduction

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The objective of this work is to implement a system that integrates pre-interventional Magnetic Resonance (MR) and real time Transrectal Ultrasound (TRUS) imaging to support image-guided procedures, for the diagnosis and treatment of Prostate Cancer (PCa). The system is based on image processing tools, shape modelling and registration algorithms, and provides accurate positioning of the prostate and cancer sites, enabling focal needle navigation, as in biopsies, brachytherapy, cryotherapy, and also with potential application in HiFU - High Intensity Focused Ultrasound.

In this introductory chapter, in Section 1.1, the problematics of PCa are laid out, followed by the main diagnostic tools and the role of MR imaging, regarding its efficacy in estimating cancer position, size and grade, that is presented in Section 1.2. Then, in Section 1.3, an overview of the principal therapies used in PCa is given, leading to the discussion about future perspectives in the PCa management in Section 1.4. In Section 1.5, the state of the art in MRI guided prostate interventions, US segmentation and MR/TRUS image fusion is presented, supporting this work’s proposed approach which is introduced in Section 1.6. Finally, the outline of the remaining work is presented in Section 1.7.

1.1 Prostate Cancer - The disease

Prostate Cancer is the disease where cancer, the proliferation of abnormal cells, is located in the prostate gland [1]. The prostate is a small walnut-sized organ located at the base of the bladder and wrapped around the urethra. It’s an exocrine gland that takes part in the male reproductive system and is mainly responsible for producing the liquid part of the semen [2]. Its structure can be divided in four main zones: the central zone, the peripheral zone, the transition zone and the anterior fibromuscular zone. The most prone to cancer is the peripheral zone, located in the posteriolateral part of the prostate, which accounts for 70% of the gland volume and is the origin of 70-80% of prostatic cancers.

![Illustration of the prostate anatomy](a), image from www.zmescience.com, and its division in four zones b), image from www.pathologyoutlines.com.

PCa is normally a slow developing cancer, that takes some years to become large enough to be
detectable and even longer to spread beyond the prostate. However, there are also some cases of fast developing more aggressive cancers, making the correct diagnostic and treatment of this disease hard and demanding [1].

According to some estimates in Europe [3], PCa is the most common of all the non-skin cancers, representing 22.2% of all the cancer cases and being the third in number of deaths (with 9.9% of all cancer deaths). In 2008, 382 thousand cases were estimated in Europe and 89 thousand deaths related to PCa. Similar studies in the United States [4] support that PCa is the most common cancer, responsible for 28% of the estimated new cases in 2010 and 11% of the cancer deaths.

Figure 1.2: Prevalence of PCa in autopsy cases with increasing age according to [5]. The white and black bar account respectively for insignificant and significant tumour sites by histological definition and $n$ is the number of patients in the study.

The probability of developing PCa increases with the age, being relatively rare below 40 (0.01%) and more common above 70 (12.48%), as can be seen in Figure 1.2, resulting in an overall probability of developing invasive PCa form birth to death of 15.90% (approximately 1 in 6) [4]. As the population is aging in more developed countries, it is likely that more and more persons may develop PCa and this value may increase. According to current urology guidelines [6], the main risk-factors for developing PCa are increasing age, ethnic origin and hereditary.

Although the frequency of autopsy-detected cancers is roughly the same in different parts of the world, the incidence of clinical PCa differs widely between different geographical areas, being high in the USA and Northern Europe and low in Southeast Asia. African Americans usually have higher incidence rates than whites and higher mortality (Figure 1.3). As for heredity, if one first-line relative has PCa, the risk of developing the disease is at least doubled. If two or three first-line relatives are affected the risk can increase 5 and 11 times respectively. Exogenous factors may also affect the risk of progression from so-called latent PCa to clinical PCa such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation and chronic inflammation.

Observing the Figure 1.3, where the incidence and mortality rates of PCa over the years are shown, one can see a big increase of the incidence in the late 1980s. According to some authors [5, 7], this increase were due to the large number of cases detected once Prostate Specific Antigen (PSA) blood tests became available in routine exams and the possibility of anticipated diagnoses that the test introduced. This fact also lead to a small increase in mortality, as bigger number of deaths were attributed to PCa. However, in the past decade, a small dip in mortality has been verified, and is likely
related to the advancements in the treatment of the disease, such as the wider adoption of radical prostatectomy and a more widespread and rational use of combined radiotherapy and antiandrogen therapies for patients with locally advanced disease [7].

Figure 1.3: Age-adjusted total US incidence and mortality rates for prostate cancer, Age-adjusted to the 2000 US Std Population [5].

1.2 Diagnosis

Current diagnostic tools to obtain evidence of PCa include Digital Rectal Examination (DRE), serum concentration of PSA and transrectal ultrasonography (TRUS). However, the definite diagnosis depends always on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens [6].

DRE is an exam where the clinician palpates the prostate through the rectal wall. Since the peripheral zone of the gland, where most prostate cancers are located, is posterior and in contact with rectal wall, it’s easy for the physician to find suspect masses and abnormalities. In 18% of all patients, PCa is detected using this exam and a suspicious DRE is usually a strong indication for prostate biopsy as it is predictive for more aggressive PCa [8, 9].

As seen in the previous section, the introduction of PSA in routine exams has played a big role in PCa diagnosis. PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. It is organ-specific but not cancer-specific and serum levels may also be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. Normally the higher the PSA level, the more likely the existence of PCa. As an independent variable, PSA is a better predictor of cancer than suspicious findings on DRE or TRUS. The increased use of PSA has improved early detection of PCa increasing the proportion of pathologically localized curable cancers. However, this exam has also introduced a high risk of overdiagnosis, as some low-risk cancers that would have never been life-threatening are diagnosed, resulting in clinical interventions that can cause harms and cost related to treatment that might have been unnecessary [10]. An intense debate in all major urological societies has been running both in US and Europe about the rational use of PSA screening and the net benefit of standardized screening programs comparing to opportunistic screening.
Another tool used in diagnosis is the transrectal ultrasonography, where an ultrasound probe is used to analyse the prostate. In a classic exam an hypoechoic area in the peripheral zone may be indicative of PCa. Still, gray-scale TRUS does not detect areas of PCa with adequate reliability, and is therefore not useful to replace systematic (but randomized) biopsies of the full prostate with targeted biopsies of suspect areas [6].

Based on PSA level and/or a suspicious DRE, a prostate biopsy may be needed for histopathologic confirmation and biopsy is currently the only way to confirm a PCa hypothesis. The standard method is to perform TRUS-guided systematic biopsy. In this procedure a 2D US probe is equipped with a needle guide for transrectal (through the rectal wall) access to the prostate. The needle trajectory is aligned with the TRUS image enabling the visualization of the needle trajectory and placement (Figure 1.4(a)). Since some lesions are isoechoic, thus not visible in US images it is necessary to sample the prostate in a systematic randomized way. The gland is usually divided into six or more zones of equal volume and one or more core is randomly collected from each zone. In initial biopsies, the needles are usually laterally directed to the peripheral zone, since 70% of the lesions are situated in this area. These samples are later analysed in laboratory for evidence of cancerous tissue. Although a large number of biopsies are done with a transrectal approach, as explained above, some urologists prefer to use a transperineal approach. In this case, the image is still acquired by TRUS, but needle insertion is done through the skin between the scrotum and the anus (Figure 1.4(b)). This procedure is carried out with the patient under local or general anaesthesia. Apart from the differences between the two approaches, similar detection rates have been reported in literature [11].

Figure 1.4: Illustration of the prostate biopsy procedure using transrectal a), image from National Cancer Institute (www.cancer.gov), and transperineal approach b), image from Department of Urology Oxfordshire (www.duo.oxfordshire.org.uk/).

Nevertheless, this technique presents some drawbacks. Because the cores are sampled in a blinded way, without the aid of any visual references (in particular with respecto to 3D space), it’s very difficult to know the correct position of the biopsy inside the gland. Therefore, it’s impossible to sample the exact same site in a later exam to investigate the development of a small cancer lesion over time and limiting the ability to adopt an active surveillance approach as will be discussed in the
next section. Furthermore, with the current technique, it is possible to miss the cancer site since the exam performs a non-exhaustive systematic search for an invisible target. This results in a low detection rate of about 30 to 40% in traditional 12-core biopsies and even with saturation biopsies with 18-cores similar results have been obtained [12, 13]. Even after an initial extended biopsy, followed by a second, third, and fourth saturation biopsy, PCa was still detected in 18%, 17%, and 14% of patients, respectively [13]. Being so, a large number of false negatives are inherent to the process, and a negative result cannot exclude cancer diagnosis. Patients with maintained suspicions may have to repeat biopsy series.

1.2.1 The role of MRI

Due to the limitation of US, in the last few years, interest has been increasing on the use of Magnetic Resonance Imaging in the diagnostic of PCa. Multiparametric MRI exams can provide information not only about the anatomy of the organ, as seen in regular T1 and T2-weighted images, but also about the physiology and chemistry of the organ. In standard T1 and T2-images, the difference in the spin relaxation time of the various tissues in the presence of a strong magnetic field is measured, and as different tissues normally have different relaxation times (T1 and T2) an intensity based image can be acquired giving anatomical information and capturing the abnormalities of cancer sites. In multiparametric images of the prostate, other magnetic image techniques are also used such as Diffusion Weighted Imaging (DWI), Dynamic Contrast Enhanced (DCE) and Magnetic Resonance Spectroscopy (MRS) [14].

DWI introduces gradient fields in order to measure phase shifts in moving molecules, therefore allowing the mapping of the diffusion process of molecules, mainly water, in biological tissues. Molecular diffusion in tissues depends on the obstacles present, such as macromolecules, fibers, membranes, etc, revealing microscopic details about tissue architecture, either normal or in a diseased state. To capture diffusion and relaxation effects on image contrast, one may obtain quantitative images of the Apparent Diffusion Coefficient (ADC). Cancerous lesions will have several tissue architectures differences that can be noticed in DWI.

The second MRI technique used in PCa is DCE MRI. In this type of image, an intravenous contrast agent is injected in the patient, usually gadolinium-DTPA (Gd-DTPA), allowing functional information such as tumour perfusion and capillary vessel leakage to be examined.

Finally, MRS enables the study of the specific resonance frequencies absorbed by a sample or tissue. These frequencies are related to the specific molecules present and can therefore be used to detect the concentration of the molecules of interest. This techniques measures the magnetic spectrum in a specific place inside the organ and is usually focused on a suspicious lesion.

In a multiparametric MRI exam, PCa lesions show as a well-circumscribed or irregularly contoured round- or ellipsoid-shaped low-signal-intensity lesion, both in T2 and DWI [15]. In DCE imaging, PCa usually presents an early intense enhancement with rapid washout. As for MRS, an increased value of the ratio between the choline and citrate molecules are usually a strong indication of cancerous tissue [16].
A recent work trying to find histopathological correlation between multiparametric MRI findings, achieved a positive predictive value in the peripheral zone using all 4 MRI sequences of 98% and 97% in central zone, much higher than exams of T2-weighted alone which had 69% and 87% respectively [17]. These results support the fact that MRI may play a strong role in PCa detection and a recent European consensus meeting concluded that it’s a high potential tool in the diagnostic pathway for prostate cancer after being validated in more prospective trials [18].

1.3 Therapy

As seen in last section, any PCa suspicion must be histopathologically confirmed by a prostate biopsy with the inherent uncertainty about the lesion location. Therefore, almost all PCa therapies suggested in the European guidelines are whole gland directed which frequently has side effects such as impotence and/or incontinence. In this section a brief description of the main treatments currently used is discussed, based on the 2012 European Association of Urology guidelines for PCa [6].

The most common therapy for localized PCa is Radical Prostatectomy (RP). RP is the surgical treatment which involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. This procedure is normally accompanied by bilateral pelvic lymph node dissection, in order to eliminate any cancerous cells that may be retained there.

RP can be performed through open incisions, in a retropubic or perineal approach, or with minimally invasive procedures such as laparoscopic radical prostatectomy and robot-assisted laparoscopic prostatectomy, namely the da Vinci surgical system. The robot-assisted procedure is becoming the gold standard surgical approach for clinically localised prostate cancer in the United States and is also being increasingly used in Europe and other parts of the world. Comparing the results between open incisions and laparoscopic approaches, it has been concluded that the second are followed by significantly lower blood loss and transfusion rate, but the available data are not sufficient to prove the superiority of any surgical approach in terms of functional and oncological outcomes [19]. This approach is normally advised for low and intermediate risk localised PCa with a life expectancy of more than 10 years, and some high risk cancers. If performed by a experienced surgeon satisfactory quality of live can be achieved. Nevertheless, slight incontinence and impotence may result from this procedure with incidence of 15-50% and 29-100%, respectively [6].

One non-surgical approach is radiation therapy, that can be applied both with an external beam or with internal radioactive implants (brachytherapy). At present there are no randomised studies comparing RP and radiation therapy, however, National Institutes of Health (NIH) consensus of 1988 state that external irradiation offers the same long-term survival results as surgery.

In an external beam radiation therapy (EBRT), anatomical data is acquired by scanning the patient, using Computed Tomography (CT) or MRI, in a treatment position, and transferred to the 3D treatment planning system, which visualises the clinical target volume and then adds a safety margin. At the time
of irradiation, a multi-leaf collimator is programmed by the planning system and adapts to the contours of the target volume seen by each beam. Real-time verification of the irradiation field by means of portal imaging allows for comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. Although the radiation used is normally electromagnetic, new innovative techniques using protons and carbon ions beams are currently being explored.

**Figure 1.5:** Illustration of the brachytherapy procedure, image from Mayo Foundation (www.mayoclinic.com).

As for brachytherapy, a transperineal method is used with an TRUS system for needle navigation and planning. The patient is undertaken under general anaesthesia and positioned in a dorsal decubitus gynaecological position. The ultrasound probe is fixed to a positioning system with 2 degrees of freedom, rotation and translation, and introduced inside the rectum, enabling the acquisition of the prostate volume. Then, the surgeon delineates the prostate boundaries and a physicist performs a real-time dosimetry and needle planning. The radioactive seeds, normally containing iodine-125, are then inserted by a radiologist according to plan. Figure 1.5 illustrates the whole procedure.

Possible consequences of radiotherapy procedures are late genitourinary or gastrointestinal toxicity, as well as some impact of irradiation on erectile function although in a lesser degree than surgery. A recent study has also demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following this type of treatment [20].

Hormonal therapy is another possibility in the treatment of PCa, since prostate cells are physiologically dependent on androgens (hormones responsible for male characteristics) to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells [21]. The testicles are the source of most androgens, with adrenal biosynthesis also providing only 5-10% of androgens. Testosterone is secreted in testes and is regulated by the hypothalamic-pituitary-gonadal axis through other hormones. Within the prostate cell, testosterone is converted to 5α-dihydrotestosterone (DHT) that is an androgenic stimulant about 10 times more powerful than testosterone. Meanwhile, circulating testosterone is peripherally aromatised and
converted to oestrogens, which, together with circulating androgens, exert a negative feedback control on hypothalamus. If prostate cells are deprived of androgenic stimulation, they undergo apoptosis (programmed cell death). Any treatment that results ultimately in suppression of androgen activity is referred to as androgen deprivation therapy (ADT). Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens by surgical or medical castration or inhibiting the action of circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens. These two methods of androgen deprivation (surgical or medical castration and the use of anti-androgens) can be combined to achieve what is commonly known as complete androgen blockade.

The side-effects of hormonal therapy depend on the strategy used (castration and/or mechanism of inhibiting the action of hormones), but loss of libido and erectile dysfunction are usually recurrent. Other systemic side-effects are bone problems, obesity and sarcopenia (loss of skeletal muscle mass), lipid alterations and insulin resistance, metabolic syndrome, diabetes, cardiovascular disease and worse emotional functioning.

Two alternative therapeutic options have recently emerged that have potentially the same therapeutic efficacy as established surgical and non-surgical options, with reduced therapy-associated morbidity. These are the cryosurgery and high-intensity focused ultrasound (HIFU). The first is already recognized as therapeutic alternative according to the guidelines of the American Urological Association, on the other hand, HIFU is still considered experimental.

In cryosurgery or cryotherapy, the setting is similar to brachytherapy and also uses TRUS guidance, however, instead of introducing brachyneedles for radioactive implants, cryoneedles are inserted resulting in temperatures of \(-40^\circ C\) inside the prostate. In order to preserve urethral function a warmer is generally introduced inside the urethra. This freezing technique may induce the cell death by four different ways: dehydration resulting in protein denaturation; direct rupture of cellular membranes by ice crystals; vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemia and by apoptosis. This technique is currently indicated for low-risk patients and there's currently only minimal data about the long-term outcome for cancer control at 10 and 15 years. Despite some major harms as incontinence and urinary retention are minimized with this kind of therapy, erectile dysfunction remains a consistent complication of this procedure, occurring in about 80% of the patients.

As regards to high-intensity focused ultrasound, consists of focused ultrasound waves emitted from a transducer, which cause tissue damage by mechanical and thermal effects as well as by cavitation. The goal of HIFU is to heat malignant tissues above \(65^\circ C\) so that they are destroyed by coagulative necrosis. HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position. However, this procedure is time-consuming, with about 10 g prostate tissue treated per hour. Relevant statistical data about the effectiveness of this procedure is not yet available since there's a low number of treated patients. With respect to complications, urinary retention appears to be the most common. A recent study at a single clinical center showed 17% significant incontinence and 2% showed moderate to severe erectile dysfunction, however, the sample is still to small for conclusions.
A recent study of 2010 [23], analysed data from 1990 to 2008 about the primary treatment for localized PCa from 36 different clinical sites in US. From the 11 892 men analyzed, 6.8% elected surveillance, 49.9% prostatectomy, 11.6% external-beam radiation, 13.3% brachytherapy, 4.0% cryoablation, and 14.4% androgen deprivation monotherapy. Nevertheless, in many treatment plans, more than one therapy is normally used, in order to increase disease-free survival.

1.4 Future perspectives: targeted biopsies, active surveillance and focal therapy

In the previous sections, the current tools for diagnosis and treatment of PCa have been reviewed. On one hand diagnostic tools are still very inaccurate, with low detection rate and certainty about the lesion location, and on the other hand therapies are whole gland focused, leading to overtreatment of low-risk tumors and decreasing the quality of life of the patients. These fundamental limitations open the way for the development of new methodologies as outlined below.

With respect to diagnosis, the main tendency is to complement or substitute systematic blind biopsies with targeted biopsies. Taking advantage of the MRI diagnostic potential to detect relevant PCa lesions, a statistical map with the high probability cancer zones can be used to guide biopsy needles and therefore improve the detection rate of the exam. This permits improving the ability for repeated biopsies in the same site for PCa growth analysis, as well as sampling of previously unsampled regions in the case of previous negative biopsies with maintained suspicion. A very recent article about MRI-guided biopsies [24], supports that it detects clinically significant prostate cancers using fewer biopsies than in the standard systematic procedure (in an equivalent number of men). This has the obvious consequence of reduction of diagnosis of clinically insignificant cancers. Another study concluded that MRI-guided biopsies improve PCa risk stratification by obtaining biopsies that are representative of true malignancy grade [25]. Although the results are still experimental and more robust trials have to be made, this technique will play an important role in PCa management.

Active Surveillance (AS), or active monitoring, is the designation for a new approach of conservative management of PCa. Introduced in the past decade, it adopts the conscious decision not to treat the patient immediately. Instead, the patient is followed up under close surveillance and treated at pre-defined thresholds that classify progression, such as PSA level and histopathological evolution evidenced on repeated biopsies. The main aim of this procedure is to avoid the harms of other therapies and to reduce the ratio of overtreatment in patients with clinically confined very low-risk PCa, without giving up radical treatment.

Many studies have confirmed that, in well-selected patients with very low-risk disease, there was a very low rate of progression and cancer-specific death, with only a few patients requiring delayed radical intervention. Thus, active surveillance might mean no treatment at all for patients older than 75 years, while in younger patients, it might mean a possible treatment delayed for years, preserving their quality of live.
From the economic point of view for healthcare systems, AS would also be advantageous. According to Keegan et al. [26], the average simulated cost of treatment for 120,000 men initiating active surveillance with 5 years of follow-up and subsequent delayed treatment would result in per patient cost savings of $16,042 and at 10 years of follow-up followed by treatment, still resulted in a cost benefit of $9,944.

However, there are still unanswered questions about active surveillance. A recent conference about active surveillance by US National Institutes of health [27] stated that besides lacking consensus about the most appropriate candidates and optimal protocol, accuracy and consistency of pathologic diagnosis of prostate cancer was an obstacle to the technique. Therefore, a system capable of improving biopsies accuracy will be a major progress in this technique.

Another experimental therapy for PCa that may be important in the future is focal therapy. In the past two decades, there has been a trend towards earlier diagnosis of PCa due to greater public and professional awareness, and men have been identified with smaller tumours at an earlier stage, which occupy only a small part of the prostate volume, with a greater propensity for unifocal or unilateral disease [28]. The concept of focal therapy is to treat adequately the tumorous tissue, leaving non-diseased prostate tissue untreated in the hope and expectation that the genitourinary function might be preserved. Most focal therapies to date have been achieved with ablative technologies such as cryotherapy, HIFU or photodynamic therapy. However, for these patients, further treatment may be necessary in the future. Currently, the high number of random and systematic errors associated with TRUS-guided biopsy regimens means that this procedure is not sufficiently accurate for selecting candidates for focal therapy. The future success of focal therapy will depend on adequate prostate sampling at biopsy, along with accurate characterization of the spatial distribution of tumor within the prostate [29].

1.5 State of The Art

In this section, the current main solutions for MRI-based procedures will be discussed in 1.5.1. Then, the state of art of the main tools used during this work will be reviewed: semi-automatic segmentation of the prostate and registration techniques.

1.5.1 MRI-guided prostate interventions

Solutions for MRI-guided prostate interventions can be divided in two large groups: pure MRI solutions, where the whole procedure is carried out using MRI as the only image tool, and MRI/TRUS fusion solutions, where a pre-interventional MRI volume of the prostate and real time TRUS images are registered. For each group, both transrectal and transperineal interventional approaches have been proposed.

The first MRI-guided solutions for prostate interventions started to be proposed in the beginning of this century. At the time, pure MRI solutions, where the whole procedure was carried out using MRI as the only image tool, were the main subject of study. As seen in the previous section, multiparametric
MRI has better sensitivity for PCa lesions than standard TRUS system and can therefore detect high PCa probability zones. Nevertheless, due to the high magnetic fields used in MRI, most of the components commonly used in biopsies may not be used in close proximity to the scanner because of their ferromagnetic properties. Furthermore common MR systems also have a small cylindrical space for positioning the patient, which difficults the execution of a normal procedure. In order to adapt the biopsy procedure for MR guidance, two magnetic compatible end-effectors for a transperineal approach were proposed by Hata et al. [30] and Susil et al. [31]. The transperineal approach has the advantage of higher accuracy in biopsy core location and the ability to sample more tissue from the peripheral zone. However, this type of access normally requires anaesthesia, involving costs and possible side-effects for the patient other than standard biopsies. In order to outcome these drawbacks, two new transrectal end-effectors were proposed by Krieger et al. [32] and Beyersdorff et al. [33]. A fully actuated MRI compatible robot for transperineal access, called MrBot, was described in Stoianovici et al. [34] and Mozer et al. [35], where the physician does not directly control the robot but only defines the needle path and monitors its action. Although it may have high potential, this can also be a drawback since physicians usually prefer to still have control of the procedure.

The proposed approaches with pure MRI-guidance solves many of the location problems and enables targeted biopsies, achieving an accuracy of the order of 2 mm. Still, MRI systems are a costly and sparse resource in most countries, and electromagnetic compatible instruments are also more expensive than traditional biopsy ones. Therefore, it is unlikely that this solutions will become a standard for the millions of prostate biopsies performed in the US and the EU alone every year although it may become an option for repeated saturation biopsies in inconclusive results [36].

To address this problem, several groups started to research MRI/TRUS registration methods, thus taking the advantages of the two modalities. On one hand, TRUS imaging doesn’t require a special magnetic compatible environment as MRI and can be used in any surgical room, and on the other hand it is a much cheaper modality and vastly available in current hospitals.

The first solutions using MR/TRUS image fusion for the prostate were published in 2007 by Xu et al. [37], Baumann et al. [38] and Andriole et al. [39]. The first two solutions proposed to acquire a US volume prior to the intervention to serve as anatomical reference, where real time US images would be superimposed using image-based registration. Using this method, biopsy targets in the image reference system were mapped to the pre-intervention fixed volume enabling to locate the acquired biopsy cores inside the prostate. Xu acquired the 3D volume using a 2D TRUS probe with a magnetic tracking sensor to locate the acquired images in the world frame. At the beggining of the procedure, the operator would then perform a 2D axial sweep (prostate base to apex) to acquire the whole volume. The MR image and ultrasound volume were then spatially aligned by manually adjusting a rigid-body transformation. During real-time navigation, a closed-loop control algorithm would continuously register the 2D images to the reference volume using rigid transformation only. In Baumann et al. [38] the implementation of the commercial Koelis Urostation was presented. With this system a US probe with an internal articulated, motorized transducer array was used allowing the acquisition of 3D images without moving the probe, which reduces the distortions in the reconstructed
volume. A kinematic model for the probe movement was introduced to estimate the position of the probe in relation to the prostate without using tracking systems and therefore reducing hardware requirements. The registration used image-based energy minimization with rigid transformations. Andriole et al. [39] reviewed in his study the TargetScan™ system commercialized by Envisioneering Medical Technologies which uses a fixed TRUS probe, with an internal motorized side-fire array, therefore minimizing the deformation and displacement of the prostate during the procedure. The biopsy samples are then acquired using flexible biopsy needles and a motorized encoded stepper to place and track the needles. Bax et al. proposed in 2008 [40] a system using a passive mechanical arm to track and control the TRUS probe as a way to minimize prostate motion. The image acquisition was based on a set of 2D images and software to reconstruct 3D volumes.

New developments to the initial solutions from Xu et al. have been presented in [41], introducing probe correction algorithms in order to take into account higher motion of the prostate. Baumann et al. also published some developments of the Koelis system. In two articles [36, 42] an elastic registration system was developed with a deformation model. In order to compare the detection rate between systematic biopsies and MRI/TRUS directed, Pinto et al. [43] studied a solution using a magnetic tracked US probe to acquire a 3D volume and then fused the images with MRI (the method used was not presented in the article). The result is displayed in Figure 1.6 and relevant improvement has been verified, especially in the high risk group.

![Figure 1.6: Comparison of detection rate between standard 12-core TRUS biopsy alone and MRI/US fusion guided biopsy alone [43].](image)

Other authors have focused in systems using the transperineal approach. As previously discussed, transperineal procedures have the advantage of better accuracy and as needles don’t contact with the rectum, it’s easier to maintain the sterility of the procedure. The main drawback is that it usually requires anaesthesia, increasing its cost. In 2009, Ho et al. [44] presented a robotic positioning system for transperineal needle insertion using TRUS guidance. The US volume is acquired using a bi-planar US probe moving inside a plastic sheath to avoid prostate deformation. The biopsy needle is then inserted in the prostate with a robotic positioning system using a dual-cone technique where the needles are inserted through two pivot points, therefore using minimal skin puncture. In Hadaschik et al. [45], the commercial system BiopSee® by MEDCOM is analysed. This product uses a brachytherapy like approach, acquiring the US volume in a way similar to Ho et al. [44]. MRI and
US are then fused together via an automated algorithm or manually under simultaneous visualization of the US and MRI planes. According to the MRI plane the needles are inserted using a brachy-like needle-guide.

The following Table 1.1 summarizes the principal studies about MRI-based procedures along with the major features introduced in each work.

Table 1.1: Table summarizing the major studies about MRI-based procedures and their main characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Image Method</th>
<th>Medical Approach</th>
<th>Main features</th>
<th>System name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hata et al. (2001)</td>
<td>MRI</td>
<td>Transperineal</td>
<td>MRI compatible end-effector</td>
<td></td>
</tr>
<tr>
<td>Susil et al. (2004)</td>
<td>MRI</td>
<td>Transperineal</td>
<td>MRI compatible end-effector</td>
<td></td>
</tr>
<tr>
<td>Krieger et al. (2005)</td>
<td>MRI</td>
<td>Transrectal</td>
<td>MRI compatible end-effector</td>
<td></td>
</tr>
<tr>
<td>Beyersdorff et al. (2005)</td>
<td>MRI</td>
<td>Transrectal</td>
<td>MRI compatible end-effector</td>
<td></td>
</tr>
<tr>
<td>Xu et al. (2007)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Image based, 2D US with tracking system</td>
<td></td>
</tr>
<tr>
<td>Andriole et al. (2007)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Side-fire US probe and flexible biopsy needles</td>
<td>TargetScan™</td>
</tr>
<tr>
<td>Baumann et al. (2007)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Mechanical probe movement model, Intensity based, 3D Ultrasound</td>
<td>KOELIS</td>
</tr>
<tr>
<td>Stoianovici et al. (2007)</td>
<td>MRI</td>
<td>transperineal</td>
<td>Fully actuated MRI compatible robot</td>
<td>MrBot</td>
</tr>
<tr>
<td>Bax et al. (2008)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Passive mechanical arm to track US probe</td>
<td></td>
</tr>
<tr>
<td>Mozer et al. (2009)</td>
<td>MRI</td>
<td>transperineal</td>
<td>Fully actuated MRI compatible robot</td>
<td>MrBot</td>
</tr>
<tr>
<td>Ho et al. (2009)</td>
<td>MRI/TRUS fusion</td>
<td>Transperineal</td>
<td>Robotic needle positioning system</td>
<td></td>
</tr>
<tr>
<td>Xu et al. (2009)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Introduced motion correction to previous algorithm</td>
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</tr>
<tr>
<td>Hadaschik et al. (2011)</td>
<td>MRI/TRUS fusion</td>
<td>Transperineal</td>
<td>Brachytherapy like biopsy procedure</td>
<td>Biopsee®</td>
</tr>
<tr>
<td>Baumann et al. (2011)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>Improved elastic Registration procedure</td>
<td>KOELIS</td>
</tr>
<tr>
<td>Pinto et al. (2011)</td>
<td>MRI/TRUS fusion</td>
<td>Transrectal</td>
<td>-</td>
<td></td>
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</tbody>
</table>
1.5.2 Prostate Segmentation in US

The segmentation of the prostate into a US volume is required for the registration method implemented in this work. Manual segmentation is still the most used nowadays. Nevertheless, it is a tedious and time consuming process and many automatic and semi-automatic methodologies have been proposed. The prostate segmentation in TRUS is a very demanding task, mainly due to the low contrast of the images, the speckle noise, micro-calcifications and shadow artefacts that are many times associated with this imaging modality. The most important solutions found in the literature may be globally categorized in two different groups: the contour and shape based methods and the classification based methods [46].

The first group uses the features in the boundary and the information of the shape to perform the segmentation. This can be done using edge based methods, like in other fields of image processing, by analysing the image with gradient filters. However, due to the frequent noise and artefacts of the US images, it often detects false edges and also broken boundaries and therefore must be implemented together with noise reduction filters. Examples of this approach are the ones implemented by Kwoh et al. [47], Aarnink et al. [48] and Pathak et al. [49].

Other techniques that still fall in the first group are the ones based in deformable models such as active contour models, deformable meshes and active shape models. This type of segmentation introduces geometrical constraints to the model shapes and then optimizes it to better fit the observed data. The implementation is often performed by imposing both external energy, that attract the contours towards the image boundary, and internal energy that preserves shape smoothness and acceptable formats. Active contour models (ACM), also called snakes, start with an initialization of the contour and then search for the correct boundary by following the direction of the gradient of the image. This method has been applied to the prostate segmentation by Ladak et al. [50] and Ding et al. [51]. This method may be extended to 3D by using deformable meshes instead of contours, that evolve from an initial shape and then deform in order to minimize internal and external energy. Nevertheless, the use of these methods without prior shape knowledge normally tend to produce models far from the anatomical structures. Active shape models (ASM) overpass this problem by leveraging on prior information of the prostate shape to guide the deformable contours. This information about the shape is normally obtained by principal component analysis (PCA) to a training set of shapes to create a statistical shape model (SSM). This method normally drives better results, as it is more robust to noise and artefacts. This method has been used in the literature by Shen et al. [52], Hodge et al. [53] and more recently by Yan et al. [54], and was the one chosen to be implemented in this work.

Classification methods define measurable pattern recognition features that are used to discriminate different regions. The objective is to obtain a partition of the vector space associated to those features, the feature spaces, creating different regions with given labels. This can be performed both using classifiers, where a labelled training set is analysed in order to create a predictor that is capable of classifying new observed data and assign a label to it, or using clustering methods, where instead a set of unlabelled feature vectors is given and are then grouped in different clusters accord-
ing to similar feature vectors. An example of the classifier approach is the work of Zaim et al. in [55] that used neural networks with texture features, spatial information and gray-level values, and [56] where a multiwavelet kernels with support vector machines (SVM) was used. Also using classifiers, Mohammed et al. [57] used multiresolution Gabor filters in SVM for the prostate segmentation. As regards clustering, Richard et al. [58] used an automated procedure to label each pixel in the image as internal or external to the prostate, based in four texture energy measures.

1.5.3 Registration

Multi-modality image registration is currently a large field of study and different approaches have been studied to solve it, differing in the imaging techniques, type of transformations used (rigid or elastic) and the necessity of landmarks or segmentation. The objective of the image registration algorithms is to establish a relation between images. In this section, the main methods applied to the prostate are discussed.

One class of registration methods is based in Finite Elements Analysis (FEA). FEA is a widely used numerical technique to solve problems in mechanical systems governed by partial differential equations. This method models tissues according to properties, such as specific mass, modulus of elasticity and Poisson’s ratio. In this way, based on a system shape, boundary conditions and external loads, one can estimate the tissue motion and deformation both statically and dynamically. Thus, these registration transformations are more general and potentially more realistic than rigid ones. In 2002, Mohamed et al. [59] presented a work where they applied this technique in order to estimate the prostate deformation during a brachytherapy procedure. They used a patient specific biomechanical model to simulate different TRUS probe insertion angles and depths, then extracted the main modes of the deformation of the prostate using principal components analysis (PCA) (this method will be explained latter in chapter 2.3.1), and used this information to establish a deformable registration between 2 orthogonal cross-sectional ultrasound images and the preoperative prostate model. More recently, two different works from Hu et al. [60] and Taylor et al. [61] used statistical shape/motion models, trained using FEA, to predict and compensate gland deformation due to TRUS probe pressure achieving very good results.

Another registration technique is performed using Thin-Plate Splines (TPS). TPS is a very fast and general method that gives realistic deformation fields that outperform rigid registration. This method is essentially an interpolation method based on the direct registration of corresponding landmarks in two different datasets, that calculates a transformation function which establishes the match between those landmarks and smoothly interpolates it to the rest of the space. The correspondence between the landmarks may be determined manually or with an automatic algorithm. Several authors studied the application of TPS to estimate prostate deformations. Venugopal et al. [62] and Cheung [63] used this method to relate two different MRI datasets with and without the endorectal coil inflated and found the algorithm robust. Makni et al. [64] applied TPS to MRI/TRUS fusion of clinical images acquired from biopsy studies, achieving a small residual error and robust performance. This registration technique will be the one used in Section 3.3 of this work.
A different approach to registration used the methods based in Mutual Information (MI). MI methods attempt to align two different image modalities optimizing a function that measures the agreement between the two image modalities, i.e. the degree to which the information content of one image set is contained in or is explained by the information content of the other. Depending on the function chosen it can be used for aligning images from the same modality or from different modalities. This method was used in the prostate by Xu *et al.* [37] and Baumann *et al.* [38] discussed above.

Nevertheless, this research topic is still in an experimental phase and no current strategy has yet proven to be the ideal one.

### 1.6 Proposed Approach

As seen in the previous section, many different approaches for the registration between MRI and US can be adopted and many solutions have been proposed in the last few years for the prostate.

The main objective of this work was to study and develop a tool for MRI/TRUS image registration for the brachytherapy procedure that would continuously superimpose on the intra-procedural TRUS images the lesion locations identified in the MR images. During the development phase, this tool should be able to work in parallel to the current procedure, without affecting it, allowing continuous validation by the medical team.

In the current procedure, manual segmentation of the prostate is performed on the axial TRUS images, from which a 3D volumetric model is then obtained and the radioactive seed dosage calculated. A closed commercial software tool is used throughout this procedure.

The improvements to the current procedure which are proposed in this work are twofold. The first improvement is to implement semi-automatic prostate segmentation, contributing to a faster execution of the procedure while still keeping the medical team hands-on. This enables their full supervision, taking advantage of their medical expertise. The second improvement is to overlay on the TRUS images the location of the lesions obtained from the MRI, thus allowing the visualization of their relative position to the radioactive seeds.

For the registration procedure, both MRI and ultrasound images have to be analysed. MRI images are acquired before the procedure, and since it’s a multiparametric dataset, different exams have to be analysed by the urologist in order to find and classify the suspected lesions. Although there are some MRI semi-automatic segmentation techniques described in the literature, as the one proposed by Flores-Tapia *et al.* [65] based on wavelet multiscale products and the software developed by Vos *et al.* [66] for automatic detection of PCa suspicions based in the multiparametric MRI, one has decided to keep this step manual. The implementation of such a system would be very time consuming and would deviate from the main purpose of this work. Therefore, the image processing was focused on TRUS images since they have to be processed during the procedure, where time-constraints are important and semi-automatic analyses are required for real-time needle navigation.

Therefore, the first step was the development of the TRUS segmentation used during the procedure, creating semi-automatic and supervised automatic algorithms that help the normal procedure
and enable faster segmentation. Since US image segmentation is strongly influenced by the quality of the data and its artefacts, such as attenuation, speckle noise, shadows, and signal dropout, normal edge-detection algorithms tend to fail. In order to address this problem, a method involving prior knowledge of prostate shape had to be used. The implemented method is based in active shape models as the ones found in Hodge et al. [53] and Yan et al. [54], and required the implementation of Statistical Shape Model (SSM) from the studied patients.

In the proposed approach, the segmented contours from both MRI and TRUS datasets were interpolated in 3D using Radial Basis Functions (RBF) to create implicit surfaces and three dimensional meshes. For the registration process, a feature-based non-rigid registration method was used based on Chui and Rangarajan [67] and Makni et al. [64]. At first, a rigid registration is performed using an Iterative Closest Point (ICP) algorithm, then an elastic deformation is estimated using TPS. The registration is then visualized by creating fusion images superimposing the two modalities fused together, as well as any segmented region of interest (ROI) in the MRI, such as a cancerous tissue.

In Figure 1.7, a schematic illustration summarizing the different steps performed during the registration procedure is shown. The framework developed was designed to be general enough to be extended to biopsy exams as well as other prostate applications. At the end of this work, a preliminary study of the biopsy procedure is presented. The image acquisitions were performed free-hand and
the US probe position and orientation were tracked with an optical tracking system. The developed reconstruction algorithm was also used here, and it allowed to uncover very large prostate motions and deformations during the procedure due to the anaesthetic fluid and the forces imposed by the probe. For these patients, MRI data was not available as currently it is not part of the standard diagnostic procedure. In fact, this work falls under the scope of a broader project led by the involved physicians, which targets the introduction of MRI in prostate cancer diagnosis for active surveillance and focal treatments.

1.7 Thesis Outline

The body of this thesis is organized in the following way: in chapter 2 the image processing and the segmentation process is presented, covering US images filtering, the manual segmentation and the implementation of the semi-automatic segmentation algorithm. Then, chapter 3 will focus on the registration methodology, covering the mathematical formulation of the model reconstruction using RBFs, the rigid registration algorithm and the fundamental of the thin-plate splines and its application to elastic deformation. Chapter 4 introduces the application of the previous tools in the brachytherapy and presents the main results. Following, chapter 5 presents the study developed for localizing biopsy cores inside the prostate for biopsy exams. Finally, the conclusions driven from the experimental work and its appliance to the diagnosis and treatment of PCa will be addressed in chapter 6.
2

Image Processing and Analysis

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In this chapter the US image processing techniques studied and implemented in this work are presented. First, the initial filtering for denoising the US images is discussed in Section 2.1. Then, the tool developed for manual segmentation is explained in Section 2.2. In Section 2.3, the segmentation algorithm using ASM is laid out, with its basic concepts and mathematics such as SSM and the image searching procedure.

2.1 Image Filtering

Ultrasound images are usually known for their relatively low image quality as they contain artefacts such as attenuation, speckle, shadows, and signal dropout which complicate the segmentation task, contributing for example to missing feature boundaries. In order to overcome this issue, noise removal is normally a required step in US segmentation.

Speckle noise is the most important artefact in US images and is responsible for their characteristic granular appearance. This type of noise is related to coherent imaging and has been studied not only in medical ultrasound imaging but also in optical (such as LASER) and radar imaging [68]. Although the texture observed in speckle noise isn’t related with the structure of the observed tissue, its pattern of local brightness is related to the local echogeneity of the underlying scatterers. In US imaging the received echo signals that create the image are obtained by a coherent summation of echo signals from many ultrasound scatterers. Speckle has both a random and deterministic origin as it is formed from backscattered echoes of randomly or coherently distributed scatterers in the tissue and the statistical properties of the signal depend on the spatial distribution of the scatters [68, 69]. The most common statistical model to describe this effect is the Rayleigh distribution [69] and is therefore used to design more effective US filters.

The objective of reducing the speckle noise is to enhance the signal to noise ratio while preserving the edges and other important features. The US filter may be classified in adaptive or non-adaptive, depending if it adapts its weights across the image as a function of the noise level or if the same filter and weights are used across the whole image, such as mean and median filters. Non-adaptive filters are simpler and easy to implement, requiring low computational power. However, they tend to lose high frequency information, specially the mean filter, making it undesirable for segmentation procedures. With respecto to adaptive-filters, they incorporate information about the statistical nature of the speckle noise and transform the multiplicative noise in additive noise for easier removal. They are based on the assumption that the mean and variance of the pixel of interest is equal to the local mean and variance of some pixels in the neighbourhood of the pixel [70]. Some examples of these filters are the Lee filter, the Gamma-MAP (Maximum a Posteriori) and the Frost filter [70, 71].

Another approach to design ultrasound filters is using Bayesian frameworks, in order to well pose the naturally ill-posed problem of reconstructing an image based in noisy observations [72]. This is done by using a priori information about the image to be reconstructed. Therefore, using this framework, the image reconstruction process is performed by minimizing a two-term energy function. While one of the terms optimizes the solution based on the observations, the other, called prior
term, smooths the image by removing ambiguities that may be caused by the first term. Throughout this work, the filter developed by Seabra et al. \cite{72} has been adopted, through the software implementation supplied by the author. This filter was chosen because it has proven very good results in de-noising US images from other human body parts, namely carotid, liver, thyroid and heart images. In his work, Seabra et al. introduces an edge preserving prior, i.e. a prior term that accounts for the distortion of transition edges of the solution related with anatomical structures, based on a log-Euclidean potential function together with a Rayleigh model of the speckle noise. The energy minimization is then performed using a Newton method, which guarantees the convergence to the global minimum of the energy function in a small number of iteration steps.

In order to illustrate the behavior of the different filters, in Figure \ref{fig:filters} one shows the image of the midgland of the prostate after applying the median, Lee and Seabra filters. As can be observed, all the filters smooth the speckle noise, however, the median and the Lee filters also smooth the edges of the prostate, making the segmentation task harder. As for the Seabra filter, one may notice that it’s not only the most effective removing the speckle noise but also preservers very well the edges of the image, resulting in a cleaner image for the segmentation process. However, the biggest disadvantage of this filter is its computation time. With the software used, it requires about 15 seconds to process each image with the filter, using a Matlab m-file implementation running in a machine with an Intel Core 2 Duo at 3 GHz and 2Gb of RAM. The Seabra filter is an iterative filter, and therefore each image is analysed several times, unlike the other simpler filters that process the image in one step with simple operations and thus require less time.

![Filters Applied](image)

**Figure 2.1:** Different filters applied to the image of the midgland region of the prostate: a) original image, b) median filter with a 15x15 neighbourhood, c) Lee filter with a 15x15 neighbourhood and d) Seabra filter.
Computational time is an important limitation for real-time image processing and although the filter may help the segmentation process, one must attend to the trade-off between performance and speed. In order to analyse that difference, a study of the automatic-segmentation algorithm with and without filter was performed and the results will be later presented in Chapter 4 for the brachytherapy.

2.2 Manual Segmentation

The first tool developed in this work was a software interface created for the manual segmentation. This interface was used for the segmentation of the prostate and regions of interest (ROIs) in the MRI images and the segmentation of the prostate in the TRUS images for the creation of the training set used for SSM and to define the ground truth to which the segmentation algorithm will be compared.

The tool created in this work tried to solve some of the problems found in the segmentation software provided with the US machine (a ProFocus 2202 by B-K medical) used during the brachytherapy procedure. Using that software, the surgeon had to use a trackball while pressing another button and delimit the whole border of the prostate without releasing the button. In this way, when accidentally releasing the button or doing a small mistake in any part of the process would result in starting all over again. Also, since the trackball is not very practical, the contour would often present sharp edges that wouldn’t correspond to the real organ, as can be seen in the Figure 2.2.

In order to overcome these obstacles, an interface has been designed where the user interactively positions control points along the image which are then interpolated using a cubic spline curve (obtained with the function cscvn of Matlab) in order to present a smooth contour. After positioning all the points, the user clicks near the first point to finalize the contour, and then he may readjust the points or translate the contour to modify the final shape. A screenshot of the interface is shown in Figure 2.3.
However, even though this interface increases the speed and commodity of the segmentation, a pure manual procedure is still very time consuming and not feasible for real-time procedures. For this reason, a semi-automatic process has been implemented, and is explained in the next section.

2.3 Active Shape Models Semi-Automatic Segmentation

Semi-automatic segmentation is very important in order to implement real-time solutions, as they are usually easier to operate and faster than manual methods. Nevertheless, even after the filtering step described in section 2.1, prostate US images are still hard to segment automatically without prior knowledge of the underlying shape. As may be seen in Figure 2.4, there are large shape variations between different axial images from base to apex. In order to deal with this variations, most authors working with prostate images are using Active Shape Models to guide the segmentation, namely Hodge et al. [53], Cosío [73] and Yan et al. [54]. ASM are based in two different components to perform the segmentation, a Statistical Shape Model of the prostate that supplies the prior knowledge of the gland shape and an image search procedure that takes the SSM and adapts it in order to fit the experimental data.
2.3.1 Statistical Shape models

The aim of SSM is to study the global shape of the prostate from a population, and use statistical tools to acquire the mean shape and principal variation modes of the gland. In this way, by examining a set of different prostates, one will be able to build a robust prior shape of the prostate that will guide the segmentation process.

To create this model, a training set is composed by manually segmented contours of the prostates in axial images of the gland from base to apex from different patients. Then, in order to have a full 3-D model, an implicit surface is created for each shape in the training set using Radial Basis Functions, as will be presented in the next chapter. This surface is then sampled in a systematic way so that each shape $s$ is represented by $M$ 3-D points as a vector, equation (2.1) where each point represents the same prostate place in all the training patterns.

$$s = [x_1, x_2, ..., x_M; y_1, y_2, ..., y_M; z_1, z_2, ..., z_M]^T$$ (2.1)

In this work, the points were acquired by sampling 10 prostate contours from the gland surface from base to apex at fixed intervals of 10% of the height of the prostate. Then 40 equally spaced points along the contour lines are collected in an anticlockwise direction as it is illustrated in Figure 2.5.
After each shape has been sampled into a $s_i$ vector, a principal components analysis is performed on the training set by calculating the mean shape vector $\bar{s}$ and the covariance matrix $C$ according to equations 2.2 and 2.3 where $N$ is the number of shapes in the training set.

$$\bar{s} = \frac{1}{N} \sum_{i=1}^{N} s_i \quad (2.2)$$

$$C = \frac{1}{N-1} \sum_{i=1}^{N} (s_i - \bar{s}) \cdot (s_i - \bar{s})^T \quad (2.3)$$

The eigenvectors and eigenvalues of $C$ are then calculated in order to find the matrices $U$ and $D$ of the singular value decomposition of $C$

$$C = UDV^* \quad (2.4)$$

The orthogonal column vectors of the matrix $U$ correspond to the eigenshapes or the modes of shape variation while the diagonal matrix $D$ stores the corresponding eigenvalues which represent the magnitudes of the shape variations. These eigenshapes are then ordered according to the percentage of the total variation they represent and a subset is chosen in order to preserve a minimum of 95% of the total. Any new shape $s$ can then be decomposed in terms of the eigenmodes using the equation 2.5 and new shapes can be generated by varying the parameter vector $b$ in equation 2.6

$$b = U^T(s - \bar{s}) \quad (2.5)$$

$$s = \bar{s} + Ub \quad (2.6)$$

During this work, fourteen different prostate shapes were acquired and used to create the training set. As will be explained in the remaining sections, the segmentation method implemented uses the statistical data from these SSMs to estimate the priors for the search procedure. Since the SSM
contains information about each shape used in the training set, the number of shapes, \( N \), and its characteristics will affect the resultant model and consequently the ASM segmentation. On one hand, if too few shapes are used, the model may be too restrictive to trained shapes and thus don’t be able to adapt to new prostate shapes, leading to segmentation errors [54]. On the other hand, Cootes et al. [74], the first developer of the ASMs, evidenced that using too much shapes may also lead to “overtrain” the model. This is particularly true if a large part of the shapes used in the model are close to the mean shape and only a few show characteristic shape variations. In that case, when choosing the number of eigenshapes to be used, the modes which best describes that characteristic shape would be truncated due to lower eigenvalue. As suggested by the author, since the training set is chosen by the user, one should choose a variety of shapes which cover the broadest range of variations that are likely to be observed, while rejecting any similar shapes. As regards the prostate, it is an organ that presents high variability of shapes and sizes, therefore, from the fourteen shapes observed in the training set, none could be classified as similar and thus one has used all the shapes in the set except the one being segmented. A similar approach was followed by [53], where all the 36 shapes studied were used except the one being analysed.

The reason to leave the one being studied apart is that the segmentation of a prostate using a SSM built using that same shape will not test the generalization ability of this tool, i.e. the performance of the tool to adapt to data acquired from new shapes out of the training set, as is evidenced in [53]. For this purpose one decided to use a leave-one-out approach when applying the ASM to the segmentation of the acquired images. Using this approach, when segmenting each US volume in the dataset, one will use all the other shapes in the training set to build the SSM except that one. In this way, one can maximize the amount of information in SSM without losing the ability to test the generalization of this tool.

### 2.3.2 Energy Function

The objective of the segmentation algorithm is to use the prior information from SSMs and based on it search the given image in order to extract the prostate contour. This deformable contour \( C \) is defined by a set of \( N \) points, \( C = \{p_1, p_2, ..., p_N\} \) that must be adapted to the image in order to minimize a certain energy functional, that measures the accordance of each point \( p_i \) of the contour to the image data. The energy function used in this work is similar to the one applied in [54] and includes three different terms as shown in equation (2.7).

\[
E(p_i) = E_{\text{image}}(p_i) + E_{\text{int}}(p_i) + E_{\text{shape}}(p_i)
\]

(2.7)

The first term in this equation is \( E_{\text{image}}(p_i) \) and is the one responsible for searching the prostate boundary features in the image and attract the contour point towards that boundary. As one can observe while looking at US images of the prostate, the inside part of the gland is usually darker (hypoechoic) than the surrounding tissue that normally is hyperechoic. This dark-to-bright transition is the boundary feature used to extract the prostate contours [53, 54]. The energy term that rules
the transition is obtained by computing the contrast of the normal vector profile as in [54], using the expression

$$E_{\text{image}}(p_i) = 255 + \frac{1}{2m}g^T f$$  \hspace{1cm} (2.8)

where $g$ is a contrast filter of the form $[1, ..., 1, -1, ..., -1]$ with size $2m$ equal to the number of points in the normal vector profile. With respect to vector $f$, it contains the intensity of the pixels along the normal vector and is calculated such that the $f_j$ element corresponds to the intensity given by the pixel at the location $x_j = p_i + n(j - m)\delta$ where $n$ is the normal vector and $\delta$ is a spacing parameter.

The second term in equation (2.7) is the internal energy of the curve that introduces continuity and curvature constraints as defined in [75] and therefore preserves the geometrical shape of the contour, penalizing discontinuities and sharp edges and resulting in smoother and more realistic shapes. The algorithm applied in this work uses the second order term and requires the two neighbour points $p_{i-1}$ and $p_{i+1}$. The internal energy term is given by

$$E_{\text{int}}(p_i) = \alpha(\|p_i - p_{i-1}\| + \|p_{i+1} - p_i\| - 2d) + \beta(\|p_i - p_{i-1}\| - (p_{i+1} - p_i))$$  \hspace{1cm} (2.9)

where the coefficients $\alpha$ and $\beta$ control the continuity and curvature respectively.

The last term is related to the shape energy and measures the accordance between the contour points $p_i$ and the prior shape obtained from SSM $p'_i$. In this way, the contour is attracted towards the prior and therefore may be useful to avoid the contour to adapt to image artefacts and strange shapes. This last term is computed as follows, where $\gamma$ is a weighting factor.

$$E_{\text{shape}}(p_i) = \gamma\|p_i - p'_i\|$$  \hspace{1cm} (2.10)

### 2.3.3 Image Search Procedure

At the beginning of the image search, the contour $C$ is initialized with the prior shape obtained from the SSM. The search procedure used in this work is performed in two different steps.

In the first step, the optimization is performed in order to minimize only the image energy term, therefore attracting the contour towards the dark-to-bright transition. This enables a quick deformation of the line in order to account for the boundary features. The search procedure is performed in order to minimize the term in equation (2.8) for each contour point. This is done via a local search around the point along the normal direction of the contour. A set of $L_{\text{search}}$ pixels are chosen along the normal, both inside and outside of the curve, and the one that presents the lower energy is chosen to be the new point location. Figure 2.6 illustrates the searching procedure followed in this step to an image filtered using the Seabra filter.
Figure 2.6: Figure showing the image search procedure in the first step of the optimization. The blue line represents the prior contour, the yellow points are the outside candidates, the green points are the inside candidates and red points are the updated contour points. The red arrow also show the normal vectors.

As regards the second step, all the terms in equation [2.7] are used. The search procedure is the same used in the first step, where the energy is minimized along the points in the normal. Since the internal energy term is second order and requires two more contour points to be computed, a full search procedure would be very demanding computationally. To minimize the energy, an iteration approach is used in this work by travelling around all the contour points several times until the points location reaches a stable location. Despite this algorithm may not reach the minimal energy, the results achieved were very satisfactory as one will see latter in this chapter with the advantage of decreasing the computing time. In Figure [2.7] one may find an illustrative image showing the difference between the contour obtained using only the first optimization step and the one obtained by introducing the internal energy and shape terms for the segmentation of an image with shadow artefacts. As one can clearly see, the image in Figure [2.7(b)] is smoother due to the internal energy and closer to the normal prostate shape.
2.3.4 Prior Estimation

The information about the prior is an important part in this semi-automatic segmentation procedure. It not only initializes the point that will be used in the local search, but also works as a constraint to the evolution of those points as a part of the energy function.

At the beginning of the procedure, in order to supply a good initialization, a mean shape of the prostate is superimposed onto the image. This contour may be scaled and adapted through some control points distributed along the line to best fit the image features. The objective is to compare that shape with the eigenshapes of the SSM, so that one can create a prior for the segmentation of the next slice based on that information. That prior will be used for the segmentation of the next contour and the resultant shape will again be compared to the eigenshapes to update the prior and so on for the remaining slices. In equation 2.5 is described the way to decompose a given shape in terms of the principal modes. In order to use it, one needs the entire vector $s$, that is created by sampling the whole volume. However, after adapting the mean shape, one only has a small part of that vector. The same happens in the remaining slices, although a newer part of the vector is obtained after each segmentation. Our aim is to reconstruct the full 3-D shape, based in a partial observation of the vector $s$. Different approaches have been proposed in the literature, namely using least square estimation of the model parameters as Blanz and Vetter [76] and Blanc et al. [77] and canonical correlation analysis as Liu et al. [78]. The first method, least squares estimation, was implemented in this work based in [76][77]. The mathematical formulation will be explained here, using the same notation as in subsection 2.3.1.

The objective is to estimate the coefficients vector $\hat{b}$ that using the eigenshapes matrix $U$, better describes the partial observation vector $r$. Taking only the reduced versions of the scaled eigenvectors in $U$ that correspond to the observation vector into a matrix $Q$, one may write the minimization problem as

$$E = \|r - Qb\|^2$$

(2.11)
However, this equation presents no constraint to the parameter vector $b$. In order to do so, and for the solution to privilege the eigenvectors with higher eigenvalues a new term is added where vector $b$ is weighted by the inverse of it eigenvalue. Equation (2.11) will be updated to the following form which is proved in [76] to be the cost function resulting from a bayesian approach

$$ E = \| r - Qb \|^2 + \lambda b^T D^{-1} b $$

(2.12)

where $\lambda$ is a regularization parameter and $D$ is the matrix with the eigenvalues in the diagonal defined in (2.4).

This expression can be expanded to

$$ E = (Qb, Qb) - 2(Qb, r) + \| r \|^2 + \lambda b^T D^{-1} b $$

(2.13)

where $(a, b) = a^T b$ is the dot product between the vectors $a$ and $b$ and therefore

$$ E = b^T Q^T Q b - 2b^T Q^T r + \| r \|^2 + \lambda b^T D^{-1} b $$

(2.14)

Differentiating with respect to $b$ and setting to zero in order to find the optimum value results

$$ 0 = \nabla E = 2Q^T Q b - 2Q^T r + 2\lambda D^{-1} b $$

(2.15)

Dividing all by 2 and grouping the terms in $b$ and $r$ writes

$$(Q^T Q + \lambda D^{-1}) b = Q^T r$$

(2.16)

And finally solving for $b$ we have the estimator for the parameter vector

$$ \hat{b} = (Q^T Q + \lambda D^{-1})^{-1} Q^T r $$

(2.17)

Using the above estimator, a tool has been implemented for creating and updating the prior for each new slice.

### 2.3.5 Segmentation process

The semi-automatic procedure implemented in this work starts by asking the user which are the limit slices at the base and the apex to adjust the mean shape to the current patient. The segmentation process is then started at the middle slice by superimposing the mean shape on top of the image with adjustable control points.

With the information about the decomposition in terms of eigenvectors one may reconstruct a custom shape and sample the contour at a different height of the prostate. Being so, one will sample a new contour that will work as the prior for segmenting the next slice. Based on that prior, the image search procedure explained in 2.3.3 will adjust the contour points to best fit the current image. The resultant contour will then be displayed to the surgeon, allowing him to adjust the final shape with
some control points. After that, the already segmented images are again compared to the the eigen-
shapes through 2.17 in order to update the prior before segmenting the next slice. This procedure
starts at the midgland slices and continues to the slices near the apex. After reaching the final image
at the apex the algorithm goes on from midgland to the base of the prostate. The pseudo-code for the
proposed algorithm follows.

**Algorithm 1:** Active Shape Model Segmentation algorithm

A.**Initialization:**
- Set the initial and final slice containing prostatic tissue;
- Select mid-height slice and superimpose mean shape;
- Adjust shape with control points;
- Estimate SSM prior with equation 2.17.

B.**Segmentation:**

for every image from midgland to apex and midgland to base do
  Create contour points based in prior ˆb;
  for each contour point do
    perform local search along the normal vector to optimize image energy in equation 2.8
  end
  for n iterations around the contour points do
    Optimize total energy in equation 2.7 along the normal vector
  end
  Enable adjustment of the contours by the user;
  Estimate SSM with the additional information from the contour;
end

The semi-automatic method proposed here enables the clinician to fully control the segmentation
process since he is the one having the last word in segmenting each frame and even if the contour is
not perfectly segmented it will spare a lot of intraprocedure time since there is still a good initialization
for the manual adjustment. The system proposed here can also perform as a fully automatic process
just by jumping the adjustment interface. In Chapter 4 one will compare the performance of the
algorithm developed here while working as fully automatic against the manual segmentation, along
with a time comparison for the automatic, semi-automatic and manual procedures.

2.3.6 Parameters Setting

The variable parameters used in this algorithm were tuned based on experimental tests and the
values used in similar studies [53 54] in order to find the most appropriate to maximize the perfor-
mance of the algorithm. During the final experiments, one has used \( N = 40 \) points in the deformable
contours. As regards to the weight factors for continuity and curvature, \( \alpha \) and \( \beta \) in equation 2.9, both
equal to 1 and the shape weighting parameter \( \gamma \) to 0.5. For the number of candidate pixels used in
the local search, \( L_{\text{search}} \), the final value used was 20 and the number of points used in each side of
the contour for calculating the contrast of the normal vector profile in equation 2.8 was \( m = 9 \).

For building the SSM of the prostate, all the fourteen acquired shapes were used for building the
training set. The number of eigenshapes needed to account for at least 95 % varied from 5 to 6
according to the eigenshapes used in the training set.
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While in the previous chapter focus was placed on image processing and the segmentation of the contours for a set of images, in the current chapter focus is placed in the registration of the two datasets. In the first section, the mathematical basics of Radial Basis Functions are presented for the purpose of interpolating the clouds of 3-D points extracted from the previously segmented images. This will render two surfaces, one for each image modality, in different coordinate systems. Then, in section 3.2 the Iterative Closest Point algorithm for the rigid registration of the two surfaces is presented. Finally, in section 3.3 the use of the Thin-Plate Splines is explained for the elastic registration step.

3.1 3D Prostate models using Radial Basis Functions

From the segmentation process, one obtains the information about the limits of the prostate in each image. The following step is then to create a 3-D cloud of points based on the information about the position of each image in a fixed frame. Since the position of each image depends on the different acquisition processes specific to a given procedure, this section will focus only on the interpolation of the 3-D clouds with an implicit surface.

In this work, the implicit representation of object surfaces with RBFs has been adopted. The advantage of using RBFs is that it offers a compact functional description of a set of surface data that enables an easy evaluation to produce a mesh with the desired resolution [79]. Furthermore, the gradients and higher derivatives of the RBFs are determined analytically and, depending on the choice of basis functions, are continuous and smooth. Therefore, the surface normals and isosurfaces are easily calculated and extracted from the implicit RBF model. This feature will be very important for the registration algorithm, where one will have to calculate the distance between the two surfaces, that will be reduced to one evaluation of a function in one point. The advantages of modelling surfaces with RBFs have been extensively documented for example by Savchenko [80] and Carr et al. showed it appliance for medical imaging in [81]. The mathematical formulation of RBFs presented here is borrowed from Carr et al.

A surface $M$ is said to be implicitly defined by a function $f(x, y, z)$ if the surface consists of all the points that satisfy

$$f(x, y, z) = 0 \quad (3.1)$$

The objective of the interpolation is to find a function $f$ which defines the surface such that all the points in the 3-D cloud are the solution of equation (3.1). However, by looking at the equation, one would easily see that the trivial solution where $f$ is zero everywhere would solve the equation without solving our problem. In order to avoid this solution, one has to append off-surface points with non-zero values such that the interpolation problem becomes

$$f(x_i, y_i, z_i) = 0 \quad i = 1, \ldots, n \quad \text{for on-surface points} \quad (3.2)$$
\[ f(x_i, y_i, z_i) = d_i \neq 0 \quad i = n + 1, \ldots, N \quad \text{for off-surface points} \] (3.3)

This different formulation creates a new problem of finding the off-surface points and the corresponding \( d_i \) value. The solution is to generate those points by projecting them along the surface normals, while setting \( f \) to be a signed-distance function where the values \( d_i \) will correspond to the distance to the closest on-surface point. These new points can be assigned in each side of the surface as can be observed in the 2-D example in Figure 3.1. Positive values are assigned to points outside the object and negatives values for the ones in the inside. Establishing points in either side of the surface leads to better results than assigning values in only one side [79]. Nevertheless, increasing the number of points will also increase the computational requirements, therefore other strategies like alternating inside and outside points may be a successful way to obtain better results without compromising efficiency.

![Figure 3.1: Creation of off-surface points along surface normals in order to set a signed-distance function.](image)

The next step is to estimate the surface normals for the cloud-points, both the direction and the sense. The strategy adopted here was to approximate the cloud-data in each point with a plane, by performing a least-square fit based on the point’s local neighbours. Defining the senses of the normals is not always an easy task and can easily compromise the final reconstruction. For complex shapes, the aligning process usually requires to travel several times along all the points in the set in order to set any neighbour points with the same sense. However, since the prostate has the shape of a deformed sphere, without any serious concave areas, one has taken advantage of this feature by requiring that the inner product between the normal vector and the vector between the cloud center of mass and the point to be positive, otherwise the normal vector would be the symmetric. After estimating the normals, one has to estimate the distance \( d_i \) for the off-surface points. The reconstructed surface is usually insensitive to this projected distance, as long as off-surface points do not intersect other parts of the surface. In Figure 3.2, three images are presented showing the estimation of the normals and off-surface points.
At this point, one has successfully acquired all the required information in equations 3.2 and 3.3. The objective now is given a set of points \( X = \{ x_1, \ldots, x_N \} \in \mathbb{R}^3 \) and set of function values \( \{ f_1, \ldots, f_N \} \in \mathbb{R} \) to find an interpolant function \( s(x) : \mathbb{R}^3 \to \mathbb{R} \) such that

\[
s(x_i) = f_i \quad \text{for} \quad i = 1, \ldots, N \tag{3.4}\]

where now \( x = (x, y, z) \) for points \( x \in \mathbb{R}^3 \).

The interpolating function is required not only to solve equation 3.4 but also to be smooth and avoid sharp transitions. This is achieved by introducing a smoothness constraint that minimizes

\[
E_{\text{smooth}} = \iiint_{\mathbb{R}^3} \left[ \left( \frac{\partial^2 s(x)}{\partial x^2} \right)^2 + \left( \frac{\partial^2 s(x)}{\partial y^2} \right)^2 + \left( \frac{\partial^2 s(x)}{\partial z^2} \right)^2 \right. \\
\left. + 2 \left( \frac{\partial^2 s(x)}{\partial x \partial y} \right)^2 + 2 \left( \frac{\partial^2 s(x)}{\partial x \partial z} \right)^2 + 2 \left( \frac{\partial^2 s(x)}{\partial y \partial z} \right)^2 \right] \text{d}x
\tag{3.5}
\]

It has been shown in [82] that the smoothest interpolants are the biharmonic RBFs. These are a particular type of RBF which have the general form

\[
s(x) = p(x) + \sum_{i=1}^{N} \lambda_i \phi(|x - x_i|), \tag{3.6}\]

where \( p \) is a low degree polynomial, the basic function \( \phi \) is a real valued function on \([0, \infty]\) and the points \( x_i \) are the centers of the RBF.

The basic functions \( \phi \) are chosen depending on the application it is directed to. For the fitting purpose of three variable functions, the most popular are the biharmonic \( \phi(r) = r \) and triharmonic \( \phi(r) = r^3 \) splines. RBFs are often used for interpolating scattered data because the associated system of linear equations is guaranteed to be invertible depending on some conditions off the locations of the data points. As regards to the biharmonic splines that will be used in this work, the condition is that data-points are not coplanar and are not required to lie in a regular grid [83]. This type of RBF is usually used with linear polynomials with the form \( p(x) = c_1 + c_2 x + c_3 y + c_4 z \) and is considered the smoothest interpolant function.
In order to limit the choice of the coefficients \( \lambda_i \) to solve the system, the orthogonality is required which implies the side conditions

\[
\sum_{i=1}^{N} \lambda_i = \sum_{i=1}^{N} \lambda_i x_i = \sum_{i=1}^{N} \lambda_i y_i = \sum_{i=1}^{N} \lambda_i z_i = 0
\]  

(3.7)

For polynomials of degree \( m \), these side conditions may be generalized to

\[
\sum_{i=1}^{N} \lambda_i q(x_i) = 0, \quad \text{for all polynomials } q \text{ of degree at most } m
\]  

(3.8)

Assuming \( \{p_1, ..., p_l\} \) as a basis of polynomials of degree \( m \) and \( \{c_1, ..., c_l\} \) the corresponding coefficients, the linear system composed by the equations 3.6 and 3.8 can be written in matrix form as

\[
\begin{bmatrix}
A & P \\
P^T & 0
\end{bmatrix}
\begin{bmatrix}
\lambda \\
c
\end{bmatrix}
= 
\begin{bmatrix}
f \\
0
\end{bmatrix}
\]  

(3.9)

where

\[
A_{i,j} = \phi(|x_i - x_j|) \quad i, j = 1, ..., N
\]

\[
P_{i,j} = p_j(x_i) \quad i = 1, ..., N, \; j = 1, ..., l
\]

and for the case of biharmonic splines with linear polynomials

\[
A_{i,j} = ||x_i - x_j|| \quad i, j = 1, ..., N
\]

\[
P_i = \{1, x_i, y_i, z_i\}
\]

\[
\lambda = \{\lambda_1, ..., \lambda_N\}
\]

\[
c = \{c_1, c_2, c_3, c_4\}
\]

By solving the system in equation 3.9 one can determine \( \lambda \) and \( c \) and therefore \( s(x) \), the interpolant function. However, the implicit surface defined by this function will necessarily pass through all the points which can be a problem when in the presence of noisy data. In the case of this work, the point cloud is not subject to noise points since they are acquired from the segmented contour. Nevertheless, if two adjacent planes are segmented in a slightly different way, the result may be a wavy surface that does not match the real structure. In that case, an approximation would result better than interpolation.

If one introduces a parameter \( \rho \), that can be thought as the stiffness, and balances the smoothness of the surface against the accordance to data, it can be shown [79] that equation 3.9 will take the form

\[
\begin{bmatrix}
A - 8N\pi\rho I & P \\
P^T & 0
\end{bmatrix}
\begin{bmatrix}
\lambda \\
c
\end{bmatrix}
= 
\begin{bmatrix}
f \\
0
\end{bmatrix}
\]  

(3.10)

Equation 3.10 is the final form used in this work for the 3-D modelling of the data from the segmentation step. One should notice that the function \( s(x) \) not only defines the implicit surface of the object, but also can be calculated in any point of the space in order to determine the isosurface that crosses that point and therefore the distance of the point to the implicit surface.
3.2 Rigid Registration using Iterative Closest Point

After obtaining the implicit surfaces through RBF interpolation one needs to find the transformation that better transforms the data from one set, US, into the other, MR. In the method proposed in this work, this objective is achieved in two steps, the first, which will be described here, establishes a rigid transformation with 6 degrees of freedom (3 translations and 3 rotations) that minimizes the mean distance from a set of points sampled from one of the surfaces and the other surface.

In order to do so, one has to choose a surface from the two modalities to be fixed and the other will be transformed to fit the first. It was chosen to fix the MRI surface because it represents the undeformed state of the prostate without any external interference. The modality to be transformed will be the surface obtained from the US images. Since the 3-D models are represented by implicit surfaces an algorithm was developed to take advantage of the fact that the interpolant function that defines the surface also represents a distance field to that surface. Therefore, the US surface was sampled into a 3-D point cloud and registered to the MRI surface. The sampling process was performed using a bounding box that encloses the implicit surface and the points were then obtained using the MATLAB function \texttt{isosurface}(X, Y, Z, V, isovalue), where X, Y and Z are 3-D matrices created by the function \texttt{meshgrid}(x, y, z), V is the value of the approximation function \(s(x)\) in those coordinates and \texttt{isovalue} is the isosurface we want to sample, in this case is 0. In the function \texttt{meshgrid}(x, y, z), x, y and z are vectors that represent the series of grid point coordinates in the x, y and z directions of the bounding box, respectively.

Given the implicit surface \(S\) from the RBF reconstruction obtained from the MRI images and a set of 3-D points obtained from the US implicit surface \(P = \{p_1, ..., p_N\}\) \(p_i \in \mathbb{R}^3\), the objective is to find the transformation \(T : p_i \rightarrow p_i'\), composed by translations and rotations along the three coordinate axis, that minimizes the mean distance from the set \(P\) to \(S\) given by

\[
E(P, T) = \sum_{i=1}^{N} d(T(p_i), S)
\]  

(3.11)

where \(d(p_i, S)\) is the distance from the \(i\)th point of the set to the surface and \(p_i'\) is the transformed point according to equation

\[
p_i' = T(p_i) = Rp_i + t
\]  

(3.12)

with \(R \in \mathbb{R}^{3 \times 3}\) representing the rotation matrix and \(t \in \mathbb{R}^3\) the translation vector.

As was emphasized, this distance can be obtained by evaluating the interpolant function that implicitly defines the MRI surface \(s_{MRI}(x)\) at the point \(p_i\) such that

\[
d(p_i, S) = s_{MRI}(p_i)
\]  

(3.13)

where \(s_{MRI}(p_i)\) is given by equation 3.6 with the coefficients obtained for the MRI interpolation.

However, since the evaluation of the function requires the computation of the distance of \(p_i\) to each center of the RBFs it would be computationally expensive. In order to eliminate this problem
and since the sampling of the mesh points along the implicit surface already requires the evaluation of the interpolation function $s(x)$ in a bounding box, the value $d(p_i, S)$ was approximated by the value that corresponds to the closest point in the bounding box. For the implementation of the algorithm, the sampling of the MRI surface into a point-cloud was also useful, since some steps are easier to perform on a point-cloud than on a surface.

The algorithm presented here is a form of a gradient descent method that searches the best solution through minimizing the cost function around the neighbourhood of certain predefined parameters, in this case the 6 degrees of freedom that define the transformation. To initialize the search an initial guess has to be provided that may influence the performance of the search in terms of computational time and final result. Since it is a local search method, it may lead to a local minimum problem where the cost function stalls in a local minimum and does not progress to the global minimum of the function. That’s another reason why the initial guess should be the most precise possibly.

As regards the translation, the algorithm was initialized by calculating the center of mass of the two point clouds and center them in the same frame, in this case in the MRI reference system. As for the rotation, since the two image modalities are acquired in a similar way (for brachytherapy) with the patient in the supine position, one has chosen a coordinate system so that the gland would be oriented in a similar way in terms of the main axis, thus providing initialization. Nevertheless, since the patient during the brachytherapy procedure is in the gynaecological position with legs high, the prostate may rotate along the sagital plane. In order to provide a better initial guess, one has implemented an optional step where both cloud points are projected in the sagital plane and a PCA is performed in each of the sets to find the principal components. A rotation that aligns the eigenvectors from both sets is then computed and the cost function is evaluated using it, in order to check if that initialization would present better results than before. If so this will be the initial transformation to be used. Figure 3.3 displays the advantage of using the PCA alignment in one of the cases studied.

![Figure 3.3: Example of using a 2-D PCA alignment for building the initial guess in ICP, comparing before with the principal components drawn a) and after b).](image)

In order to find the rigid transformation $T$ that minimizes equation 3.11 one has decided to alternate the minimization between the translations and the rotations. Using this alternate approach, one
guarantees that both translation and rotation are being optimized and may help avoid situations of local minimum. For example, if optimization is first performed for translation, the resulting points would be so adapted to the surface that no rotation would decrease the energy. Therefore, by alternating the two procedures one ensures that both are taking part in the registration.

In each iteration of the minimization process, the algorithm calculates the cost function value resulting from varying each one of the components of the transformation, \( t_x, t_y, \) and \( t_z \) for the translation and Euler angles about \( x, y, z (\phi, \theta, \psi) \) for the rotation, by a given step \( \eta \) and chooses the one with smaller cost. Since it is a coarse-to-fine approach, the step \( \eta \) decreases in each iteration in order to enable a smoother fit.

The pseudo-code for the rigid registration algorithm is given below:

**Algorithm 2: Rigid registration algorithm**

**A. Initialization:**
- Initialize translation \( t \) in order to superimpose the centers of mass;
- Initialize rotation performing 2-D PCA;
- Initialize step parameter \( \eta \);

**B. Energy Minimization:**

\[
\text{while } E_t(T, P) - E_{t-1}(T, P) > \epsilon \text{ or } t < t_{\text{max}} \text{ do}
\]

- **Translation optimization:**
  \[
  \text{for } n \text{ iterations do}
  \]
  - Evaluate cost function for the point set obtained by varying each component by \( \pm \eta_{\text{trans}} \) and choose the best
  \[
  \text{end}
  \]
- **Rotation optimization:**
  \[
  \text{for } n \text{ iterations do}
  \]
  - Evaluate cost function for the point set obtained by varying each component by \( \pm \eta_{\text{rot}} \) and choose the best
  \[
  \text{end}
  \]

\[
\text{end}
\]

The algorithm will output the transformation \( T \) that better transforms the point cloud \( P \) from the US to the MRI surface.

In Figure 3.4 the result of the rigid registration algorithm on two different patients is illustrated. As one can see in Figure 3.4(b) the TRUS probe imposes a large deformation to the prostate causing significant differences between the organ’s shape in the two sets. It is therefore necessary to create an elastic deformation step as will be explained in the next section.
Figure 3.4: Examples of the Rigid registration algorithm, the US in red and the MRI in blue. Perspective view of one patient a) and top view from another patient showing the elastic deformation caused by the probe b).

3.3 Thin-Plate Splines

In the previous section, a rigid registration algorithm has been presented. Nevertheless, a pure rigid transformation assumes that the gland may only suffer rigid body movements which for the prostate is clearly not the case. During both the biopsy and brachytherapy interventions, the gland deforms due to the physical interaction with the transducer and due to edema caused by the bleeding of some vessels. To account for the resulting shape changes an elastic registration is required.

In this work, a local parametric transformation based in Thin-Plate Splines (TPS), as proposed by Bookstein [84], has been adopted to compute the mapping between the two data sets. This method has also been used and developed by Chui and Rangarajan [67] as a tool that could be used in other different applications. More recently, Makni et al. [64] reported the application of this method to prostate with very good results, claiming a mean error of 1.2 mm in clinical trials. This method has been chosen because it is very fast and the deformation fields obtained are well adapted to the prostate. Furthermore, it doesn’t require a large training for the implementation as the statistical studies nor large computational requirements.

The mathematical basics of TPS are presented here based in [64, 67]. The principle of TPS is to compute a non-rigid mapping between two corresponding point datasets $X = \{x_1, \ldots, x_N\}$ and $Y = \{y_1, \ldots, y_N\}$. In this case, these sets will be chosen to be the US points after the rigid transformation and the MRI points, respectively, organized in a way such that each point $x_i$ in the US cloud represents the same prostate location then the point $y_i$ in the MRI prostate. Since after the rigid transformation the two cloud points are supposed to be very close to each other, the correspondences were taken so that each point $x_i$ in US would correspond to the nearest point in the MRI surface $y_i$. Then, one is looking for a function $f$ that minimizes the cost function...
\[
E = \sum_{i=1}^{N} \|y_i - f(x_i)\|^2
\]  
(3.14)

The similarities between this problem and the one in RBF interpolation are clear, despite herein one needs a function \( f : \mathbb{R}^3 \to \mathbb{R}^3 \). As already seen for the RBFs, the functions TPS were selected not only to solve the problem in equation 3.14 but also to minimize a smoothing constraint similar to the one in equation 3.5. The above cost function is therefore updated to account for that factor

\[
E_{TPS} = \sum_{i=1}^{N} \|y_i - f(x_i)\|^2 + \lambda \int \int \int_{\mathbb{R}^3} \left[ \left( \frac{\partial^2 f}{\partial x^2} \right)^2 + \left( \frac{\partial^2 f}{\partial y^2} \right)^2 + \left( \frac{\partial^2 f}{\partial z^2} \right)^2 \right] \, dx \, dy \, dz
\]  
(3.15)

The TPS model is the one that minimizes this cost and is given by

\[
f = XA + \Phi W
\]  
(3.16)

that is composed by two terms, \( A \) is a \((4 \times 4)\) matrix that represents the affine transformation and \( W \) is a \((N \times 4)\) matrix that describes the warping transformation. The matrices \( X \) and \( Y \) must be padded with a column with ones to be the form \( Y_1 = \{1, y_{1x}, y_{1y}, y_{1z}\} \) in order to be multiplied by the affine matrix \( A \). In turn, \( \Phi \) is a \((N \times N)\) radial function matrix similar to the one in RBFs and is given by

\[
\Phi_{i,j} = \|x_i - x_j\| \quad i, j = 1, ..., N
\]  
(3.17)

By combining equations 3.15 and 3.16 and introducing a regularization term to constrain the weights of the warping transformation, one can write the cost function as

\[
E_{TPS} = \|Y - XA - \Phi W\|^2 + \lambda \text{trace}(W^T \Phi W)
\]  
(3.18)

This function is minimized according to [67] by using a QR factorization to the points matrix \( X \) of the form

\[
X = [Q_1 Q_2] \begin{bmatrix} R_1 \\ 0 \end{bmatrix}
\]  
(3.19)

where \( Q_1 \) and \( Q_2 \) are \((N \times 4)\) and \((N \times N - 4)\) respectively orthonormal matrices and \( R_1 \) is upper triangular.

The final solution for the least squares minimization of equation 3.18 for \( A \) and \( W \) is

\[
\hat{W} = Q_2 (Q_2^T \Phi Q_2 + \lambda I_{(N-4)})^{-1} Q_2^T Y
\]  
(3.20)

and

\[
\hat{A} = R_1^{-1} (Q_1^T Y - Q_1^T \Phi \hat{W})
\]  
(3.21)

Finally, by applying these estimators with \( X \) and \( Y \) representing the US points after the rigid transformation and MRI points, respectively, one will have a deformation function such that any point in the US
system may be transformed in order to find its coordinates in the MRI reference. The coordinates of a point $p_i$ in the MRI reference can thus be obtained in two steps, first by calculating the coordinates $p_i'$ resulting from the rigid transformation given in 3.12 and then using the local deformation function

$$p_i'' = f(p_i') = [1, p_i'] A + \phi . W$$ (3.22)

where $\phi$ is a vector of size N with the distances between point $p_i'$ and the points in set $Y$.

In order to enable a visual interpretation of the implemented registration, an algorithm was implemented to create fused images. These images are obtained by taking the position of each pixel in an US image and, by transforming it rigidly and elastically, find the corresponding value of that pixel in the MRI image. The result is an image representing the same section of the prostate as the original US image, however, the intensity of each pixel of the image is replaced by the corresponding intensity in the MRI volume. Although the fused images, especially after the elastic deformation, may seem that it is the MRI volume that is deformed, one should remember that it is the US model that deforms to fit the MRI model.

Figure 3.5: Comparison between US image a), fused images after rigid b) and elastic registration c) and the deformation field d).
Figure 3.5 shows a midgland US image, the corresponding MRI image after rigid registration and after elastic deformation, and the MRI image with a superimposed deformation field. In order to enable the visualization of the deformation, the contour drawn in the US image is superimposed in each image and in the rigid image the deformation vectors are also displayed in red. As one may clearly observe, in Figure 3.5(b) referring to the rigid registration the contour does not match the contour in blue, specially in the area at the bottom of the figure, where the impact of the US probe is more important. However, after elastic deformation 3.5(c) one may see that is no longer the case, with the contour line matching the deformed MRI image. By observing the deformation field, red arrows in 3.5(d) and the resultant vector in three locations of the image (white arrows), one may conclude that the elastic deformation principally affects the area subject to the US probe, resulting in the tissue contracting at the probe pressure surface and the sides deforming in the opposite direction. This deformation field is very close to the one expected, with the major deformation occurring in the area of the prostate near the rectum wall, while the anterior part of the prostate (top of the images) reveals small deformation due not only to being far from the pressure site but also due to having the support of the bone. Regarding the deformation field, one may also observe a large deformation outside of the prostate, specially at the edges of the image. However, it does not have any physical relation to the underlying tissue, since the deformation is only valid inside the prostate as there were no feature points outside the prostate.

The results of applying the registration tools presented in this chapter to the brachytherapy procedure will be addressed in the next chapter, accompanied by a more detailed discussion.
4

Applications: Brachytherapy

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In this chapter, the application of the developed tools to the brachytherapy procedure is presented. In the first section, the materials and methods used are explained. Then, the results obtained for this type of application are presented and in the final section, the accompanying discussion is made.

4.1 Materials and Methods

4.1.1 Experiments

The data presented in this chapter was collected during prostate brachytherapy procedures performed at Instituto Português de Oncologia (IPO) from February to July of 2012, by the urology team of Dr. Jorge Rebola. A total of 14 procedures have been followed and the data has been recorded anonymously.

4.1.2 Brachytherapy Procedure

As has been seen in the motivation section, during the brachytherapy the patient is positioned in the dorsal decubitus gynaecological position as illustrated in Figure 1.5 and is under general anaesthesia.

At the beginning of the procedure, a set of US images is acquired using a TRUS probe and is then segmented by the urologist in order to create a shape model of the gland. During the normal procedure, using these images and a specific commercial software, the medical team plans the positioning of the radioactive seeds inside the gland and then inserts them one by one according to plan, using a needle grid.

With our system, without interfering with the medical procedure, the same US images were acquired into a laptop using a USB frame grabber. These were intra-operatively segmented and registered to the pre-operative MRI creating fusion images and calculating the transformations that map one modality to the other.

4.1.3 Multiparametric MRI

From the 14 procedures assisted, one patient had not performed a MRI exam prior to the surgery and the other had perform the MRI exam outside of the IPO, with different parameters of acquisition and poor image quality. These were both excluded from the analysis. The remaining patients had performed pelvic MRI before the intervention, with a mean time between the exam and the surgery of 64 days. The images were acquired using a Philips Intera at 1.5 Tesla without endorectal coil. T2w images and T1w images were obtained in the axial and coronal planes with a 3.6 mm spacing between slices. Dynamic ADC maps were acquired along with DCE with gadolinium as contrast agent. For the segmentation purpose, one has chosen to use the T2w axial images, because T2w is the modality that presents the best contrast for the prostate and axial slices were the ones sampled with the better resolution and presented images similar to the transversal TRUS images. The size of the T2 images used was $336 \times 336$ with each pixel corresponding to $0.6579\, \text{mm}$. 

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4.1.4 TRUS images

The US system used was a Pro Focus 2202 and the transducer used was the model 8848, both commercialized by B-K Medical. The endorectal probe is biplanar with 2 arrays, one axial and one longitudinal. During the intervention it is placed in a stepper with 2 degrees of freedom, enabling translation to adjust the probe depth inside the rectum and rotation along the probe axis. The stepper is fixed onto the operating table. Figure 4.1 displays the biplanar transducer used and its placement in the stepper.

![Figure 4.1: Images of the trandsucer model 8848 by B-K Medical showing the longitudinal and axial array a), and the transducer mounted in the stepper used in brachytherapy procedure b). Images by B-K Medical (www.bkmed.com)](https://example.com/image)

During the first two procedures, the images were saved in the system hard-disk and then moved to the PC using a USB flash storage device. For all other procedures, a USB framegrabber of the model Grabby, commercialized by Terratec, was connected to the US system through an S-video output and the images were directly imported in real-time to the software workspace. As regards to the position of the probe at the moment of each acquisition, since no tracker or encoders were attached to the probe or the stepper, they were recorded manually by the user based on the position of the stepper.
At the beginning of the procedure, a 3-D US volume was recorded by acquiring several 2-D transversal images by moving the probe cranial to caudal with steps of 5 mm until the whole prostate had been stored. Furthermore, a set of longitudinal images was also acquired by rotating the probe from $-50^\circ$ to $50^\circ$ along its main axis with an interval of $10^\circ$. The reference frame chosen for the US acquisition was based on the image obtained when the probe was set to its maximum depth. The x-axis was set to be along the height of the image with the sense up to down, the y-axis along the width from left to right and finally the z-axis along the probe axis in order to represent a direct referential, with the first image being the zero. In Figure 4.2, one may observe the two US imaging acquisition sets, the reference frame selected, the position of the US probe and the prostate model after the reconstruction.

With respect to the US images used, these have size $512 \times 444$ with each pixel corresponding to $0.155 \text{mm}$ in the axial slices and $0.126 \text{mm}$ for the longitudinal slices.

### 4.1.5 Needle positioning

During this intervention, the seeds are inserted inside the prostate using the brachyneedles according to the plan created with a commercial software. The positioning of the needles in the gland is guided by a needle grid, as can be observed in Figure 4.3(a) whose approximate positions are visualized in a virtual grid that can be superimposed on the US image 4.3(b). The depth of the needle is later controlled by moving the longitudinal transducer to a position that intersects the needle path, enabling the visualization of its path during the intervention (Figure 4.3(c)). The brachytherapy software also enables superimposing the desired position of the seed on the longitudinal image in order
to detect whether or not the needle has reached the desired position.

Figure 4.3: Images illustrating the needle insertion. A needle grid photo (image from London Bridge Urology http://www.londonbridgeurology.net) a), the grid superimposed to US image b), longitudinal image showing a brachyneedle c) and an example of needles inside the prostate model d)

The custom software designed in this work enables the visualization of the needles inside the 3-D prostate model, based on grid coordinates and the depth of the needle.

4.1.6 Registration

For the registration process, the tools described in the preceding chapters have been used in the way stated in Figure 1.7. The MRI image was acquired and segmented offline before the beginning of the intervention using the manual tool. At the beginning of the intervention the TRUS images were acquired and since both the transversal and the longitudinal images are available, one or the two may be used for the segmentation as will be later discussed. The segmentation process may be developed by using either the manual or the semi-automatic tool.

The segmented shapes from chapter 2 were then modelled using the RBFs and registered, first with the rigid model and then using the elastic deformation algorithm. The final result of the registration
can then be presented using fusion images where the two types of images are visualized as may be seen in the Figure 3.5.

4.2 Results

The brachytherapy was the main source of data for this study and was the one that guided the strategy implemented in previous chapters for the MRI/TRUS fusion. The results obtained by using the tools developed in the preceding chapters to the data collected to the brachytherapy procedure will be discussed in this section. At first, one will present the data regarding the performance of the semi-automatic segmentation algorithm and the effect of the image filters. Then the results of comparing the prostate obtained by segmenting the US images using longitudinal and axial slices as regards the different deformation imposed by the probe in the two arrangements will be displayed. Finally the rigid and elastic registration tools applied to the MRI and TRUS data will be shown.

4.2.1 Semi-automatic Segmentation

The ASM segmentation implemented in chapter 2 was applied to the axial slices of the US data acquired during the brachytherapy interventions.

4.2.1.A Evaluation Methods

In order to evaluate the performance of the segmentation algorithm explained in chapter 2 and compare against others proposed in the literature, two distance-based error metrics have been used. For enabling the comparison between different contours, the lines were sampled with the same method used for building the SSMs, by collecting 40 equally spaced points through the outline. The error metrics used were the mean absolute distance (MAD) defined by the following equation

\[ MAD = \frac{1}{N} \sum_{i=1}^{N} \| p_i - p'_i \| \] (4.1)

where \( p_i \) is \( i \)th contour point obtained from the segmented line and \( p'_i \) is the respective point from the ground truth contour, and the dice similarity coefficient (DSC)

\[ DSC = \frac{2|A_s \cap A_g|}{|A_s| + |A_g|} \] (4.2)

where \( A_s \) is the area inside the segmented contour and \( A_g \) is the area enclosed by the ground truth contour.

While the MAD measures how far each point of one set is to the others, DSC provides information of how much the segmentated area overlaps in the two contours. The evaluation of these two parameters will give a strong measure of the similarity between two different contours.

As has been discussed while introducing SSM in section 2.3.1 in order to test the generalization ability of the segmentation method, a leave-one-out approach was adopted to evaluate the results. That means that the training set of the SSM used to estimate the prior of the ASM to segment each
image set was composed by all other 13 shapes except for the one to be evaluated. In this way the SSM maximizes the amount of information without losing the generalization ability.

4.2.1.B Experimental data

Filters

In Table 4.1 one may find the MAD and DSC values resulting from the segmentation of the 14 image sets with the filter implemented in Seabra [72] and without any filter. In the presented tests, the algorithm was used in full automatic mode without the ability of the user to alter the contours.

Table 4.1: Comparison of ASM performance between raw images and images processed with Seabra [72] filter for all datasets using MAD (mm) and DSC.

<table>
<thead>
<tr>
<th>Method</th>
<th>Set-01</th>
<th>Set-02</th>
<th>Set-03</th>
<th>Set-04</th>
<th>Set-05</th>
<th>Set-06</th>
<th>Set-07</th>
<th>Set-08</th>
<th>Set-09</th>
<th>Set-10</th>
<th>Set-11</th>
<th>Set-12</th>
<th>Set-13</th>
<th>Set-14</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASM without filter</td>
<td>MAD</td>
<td>2.33</td>
<td>1.81</td>
<td>2.86</td>
<td>1.80</td>
<td>2.26</td>
<td>2.14</td>
<td>1.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.07 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>DSC</td>
<td>0.84</td>
<td>0.91</td>
<td>0.86</td>
<td>0.91</td>
<td>0.89</td>
<td>0.89</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASM with Seabra filter</td>
<td>MAD</td>
<td>2.23</td>
<td>2.15</td>
<td>3.00</td>
<td>1.85</td>
<td>2.38</td>
<td>2.38</td>
<td>1.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DSC</td>
<td>0.85</td>
<td>0.91</td>
<td>0.84</td>
<td>0.91</td>
<td>0.87</td>
<td>0.87</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It can be observed that, in average, the filtered images have a slightly lower MAD and higher DSC but the results show that the increase in performance with the adding of the filter is very small. Furthermore, in some image sets (2,4,5,6 and 12) the images without filter outperform the others. The performance of one or other depends on the properties of the images analysed. Using the filter is best when there’s high noise in the boundaries because it generally smooths the edges, however, if the edge is very badly defined, the filter destroys all the boundary information leading to poorer performance. In Figure 4.4 one may compare the segmentation obtained with the filtered image and the raw image against the ground truth on a midgland slice. This figure is an example where there’s high noise in the boundary and therefore results in the filtered image performing better than the other cleaning the noise and leading to a smoother boundary.

Either case provides good results with a DSC of near 90% and a mean distance to the ground truth of approximately 2 mm. However, since it is an iterative filter, processing the image with this filter is very time consuming. This process took approximately 15 seconds to process each image in an intel Core 2 Duo at 3 GHz and 2Gb of RAM. Comparing the performance of the ASM with and without the filter in table 4.1 and since the filtering requires a preprocessing time of approximately 10 (mean number of slices) times 15 seconds (time per slide), one may conclude that using the raw images without prior filtering is more suitable for real-time procedures.
Figure 4.4: Comparison between the performance of the segmentation algorithm with a) and without prior filtering b). The ground truth is in yellow and the automatic segmentation is in red.

The results obtained in this work were compared to the ones found in [54] where three similar methods were implemented to segment video sequences: the first, called method-1, used deformable contours using as prior the mean resulting from SSM; the second, method-2, that is more similar to the one implemented where the prior for the next image was updated based on the last segmentation; finally the ALSS that started using Method-2 but as it was applied to a video sequence it was being updated and the images were being re-segmented based on the new frames acquired. The results for this methods were MADs of 2.53, 2.01 and 1.65 and DSCs of 0.83, 0.87 and 0.91, respectively. Comparing to the results obtained in this work one may conclude that the current method outperforms method-1 and is very close to method-2, that is the one more similar to it. The last method ALSS performs better than the one implemented here, nevertheless it has access to more information since it uses several frames to segment each slice of the prostate and in the current method only one image is available. By observing the images available in the article they seem to provide better contrast for the prostate than the ones used in this work.

**Base, Midgland and Apex**

Since the visibility of the gland varies along its section, one has also compared the different performance of the segmentation along the different regions of the prostate, base, midgland and apex, separately. In the following figure one may observe the automatic segmentation at three different regions for two image sets.
Figure 4.5: Segmentation algorithm along the different regions of the gland for two datasets, base (a) and d), midgland b) and e) and apex c) and f).

The results are presented in Table 4.2.

Table 4.2: Comparison of MAD(mm) and DSC between raw images and images processed with Seabra [72] filter at the three different regions of the gland.

<table>
<thead>
<tr>
<th>Method</th>
<th>Base</th>
<th>Midgland</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASM without filter</td>
<td>MAD 2.74 ± 0.90</td>
<td>1.63 ± 0.36</td>
<td>2.31 ± 0.83</td>
</tr>
<tr>
<td></td>
<td>DSC 0.79 ± 0.13</td>
<td>0.94 ± 0.01</td>
<td>0.84 ± 0.06</td>
</tr>
<tr>
<td>ASM with Seabra filter</td>
<td>MAD 2.72 ± 0.93</td>
<td>1.54 ± 0.31</td>
<td>2.39 ± 0.86</td>
</tr>
<tr>
<td></td>
<td>DSC 0.82 ± 0.08</td>
<td>0.95 ± 0.01</td>
<td>0.82 ± 0.07</td>
</tr>
</tbody>
</table>

As expected, the performance of the automatic segmentation is best at midgland, where the gland usually presents well defined boundaries, with a DSC of 95%, which means that almost all the segmented area overlaps with the ground truth. The MAD is also better than it was for the total gland with a value around 1.6 mm. Nevertheless, the results at apex and base are rather poor, with mean distances of 2.3 and 2.7 respectively. As can be seen in the images in Figure 4.5, the image in apex presents very irregular borders and low contrast leading to worse performance. As regards to the base, one can observe in Figures 4.5(a) and 4.5(d) the presence of the seminal vesicles and the shadow on the top caused by part of the bladder, which also affect the segmentation of the images in this region.

**Time performance**

Another evaluation to the algorithm was to test the time needed for segmenting the gland. For that purpose, one has compared the time taken while segmenting the prostate automatically with ASM,
semi-automatically with ASM followed by a manual adjustment to adjust to the ground truth and the fully manual procedure introduced in chapter 2. The results may be consulted in Table 4.3.

Table 4.3: Table showing the time needed to segment the prostate using automatic, semi-automatic and manual tools in seconds.

<table>
<thead>
<tr>
<th>Method</th>
<th>Set-01</th>
<th>Set-02</th>
<th>Set-03</th>
<th>Set-04</th>
<th>Set-05</th>
<th>Set-06</th>
<th>Set-07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full automatic</td>
<td>4.16</td>
<td>4.66</td>
<td>4.75</td>
<td>4.76</td>
<td>4.76</td>
<td>5</td>
<td>3.03</td>
</tr>
<tr>
<td>Semi-Automatic</td>
<td>90</td>
<td>114</td>
<td>130</td>
<td>133.69</td>
<td>67</td>
<td>83</td>
<td>69</td>
</tr>
<tr>
<td>Manual</td>
<td>117</td>
<td>140.8</td>
<td>173</td>
<td>155.6</td>
<td>151.2</td>
<td>125</td>
<td>87.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method</th>
<th>Set-08</th>
<th>Set-09</th>
<th>Set-10</th>
<th>Set-11</th>
<th>Set-12</th>
<th>Set-13</th>
<th>Set-14</th>
<th>Av.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full automatic</td>
<td>4.48</td>
<td>5.49</td>
<td>4.27</td>
<td>4.67</td>
<td>4.14</td>
<td>4.62</td>
<td>4.21</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>Semi-Automatic</td>
<td>67</td>
<td>103</td>
<td>87</td>
<td>90</td>
<td>82</td>
<td>88.6</td>
<td>92</td>
<td>92.6 ± 15.8</td>
</tr>
<tr>
<td>Manual</td>
<td>83.5</td>
<td>142.4</td>
<td>153</td>
<td>128.2</td>
<td>111</td>
<td>125.1</td>
<td>140</td>
<td>130.9 ± 19.9</td>
</tr>
</tbody>
</table>

As can be observed in the table, the ASM performing in fully-automatic mode is the fastest with a mean time of 4.5 s. However, as has been discussed before, the fully automatic segmentation is usually not easily accepted by the clinician and is subject to the errors already seen. The semi-automatic method, where the surgeon may adjust the contour to best fit the images and the ground truth performed the segmentation in 92.6 s, sparing almost 30% of the time needed for performing the manual segmentation of the prostate with the same results.

4.2.2 Comparison between axial and longitudinal slices segmentation

As explained in the section 4.1, the US images are acquired using both axial and longitudinal images. Herein, one pretends to compare the difference between using either one and/or the other in order to create the prostate model. In order to do that, the images are segmented as in Figures 4.6 and 4.7 and then approximated using RBFs. Then the two reconstructed models are compared.

4.2.2.A Evaluation Methods

In order to evaluate the distance and the overlap of the prostate models between the two settings, and later along the different steps of the registration process, one has introduced three metric functions. The first two measure the mean absolute distance (MAD) as in equation 4.3 using two approaches to calculate the distance. One uses a point to point (P2P) method where the distance of one point in one mesh to the other is taken as the distance between that point and the closest point in the second mesh. With respect to the second, a point to surface (P2S) approach is used where the distance of each point to the surface is obtained by computing the isovalue of the interpolating function \( s(x) \) of that surface with the coordinates of that point.

\[
MAD = \frac{1}{N} \sum_{i=1}^{N} d(p_i, S) \tag{4.3}
\]

where \( MAD = 0 \) is the optimal value.

The difference between P2P and P2S is that the first measures distances between points, and is more reliable when calculating distances much bigger than the distance between two points in the MRI mesh. However, since the average spacing between points is 0.5 mm, for points very close to
the surface the distance between the US point and the closest MRI point is generally bigger than the US point to surface, resulting in a poor estimate. As regards the point to surface distance, since the interpolating function is calculated based in points at the surface and points at the 1 mm margin, it will be more precise in this margin, while the approximation will be worse for points farther away from the surface.

The other measure tool is the same already used to evaluate the segmentation performance, the DSC, but this time instead of the areas enclosed by the contours as in the equation 4.2, one will use the volume enclosed by the surfaces as

$$DSC = \frac{2|V_{MRI} \cap V_{US}|}{|V_{MRI}| + |V_{US}|}$$

(4.4)

where $DSC = 1$ is the optimal value. The DSC provides a good quantitative information about how the volumes overlap and thus a good measure of the registration performance.

4.2.2.B Experimental results

In the following Figures 4.6 and 4.7 one can observe the segmentation of the prostate using axial and longitudinal images respectively, for the same patient. Each setting has its own advantages and drawbacks. Using axial images is easier for the segmentation of the midgland slices that normally present good contrast and well defined boundaries. However, at the apex region the images have lower contrast and irregular border and are thus difficult to delimit the boundary. Another disadvantage of axial segmentation is, since the spacing between images is 5 mm, the section may change very rapidly between each slice, principally at the base and the apex, leading to some information missing and very sharp transitions between close slices. Nevertheless, these effects can be greatly minimized by using the central longitudinal image to adjust the segmentation of the slices and provide extra points in the apex and base regions.
As for the longitudinal segmentation, it provides smoother transitions from base to apex as the planes are oriented in that direction. As opposed to the axial setting, it is normally easier to delimit the apex region due to the larger amount of information available in this area compared to the axial slices where usually only one section is available. In the other hand, it is harder to distinguish the boundary of the gland in the region more distal to the US probe because there's normally shadow artefacts, mostly in the central slices, as can be seen in the slices in Figure 4.7. The segmentation is also particularly difficult in the base region because there is normally a big shadow in this area, that difficults the task of delimiting the boundary. Another major problem of the reconstruction using this type of images is that since they are radial, they are much richer in information (in this case points) in the region closer to the probe then in the area more distal, where the distance between two images is much larger.
Figure 4.7: Segmentation example using longitudinal slices.

In the following Table 4.4 one can find the results of comparing the reconstructed shapes based in the axial and longitudinal segmentations. As one can see, although the models are close to each other, it is very difficult to achieve the same exact shape using the two modalities. This is a result of the different properties of the two settings already mentioned above, that affect the final segmentation by enabling a better segmentation in some regions and poorer in other resulting in overall slightly different formats.
Table 4.4: Evaluation of the agreement between prostate models built based on axial slices and longitudinal slices, using MAD (P2P and P2S in mm) and DSC.

<table>
<thead>
<tr>
<th>Patient</th>
<th>P2P (m)</th>
<th>P2S (mm)</th>
<th>DSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.13</td>
<td>0.50</td>
<td>0.90</td>
</tr>
<tr>
<td>2</td>
<td>1.09</td>
<td>0.54</td>
<td>0.93</td>
</tr>
<tr>
<td>3</td>
<td>1.46</td>
<td>0.75</td>
<td>0.91</td>
</tr>
<tr>
<td>4</td>
<td>1.12</td>
<td>0.50</td>
<td>0.91</td>
</tr>
<tr>
<td>5</td>
<td>1.37</td>
<td>0.72</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>1.15</td>
<td>0.56</td>
<td>0.92</td>
</tr>
<tr>
<td>7</td>
<td>1.14</td>
<td>0.59</td>
<td>0.92</td>
</tr>
<tr>
<td>8</td>
<td>1.15</td>
<td>0.62</td>
<td>0.93</td>
</tr>
<tr>
<td>9</td>
<td>1.14</td>
<td>0.61</td>
<td>0.91</td>
</tr>
<tr>
<td>10</td>
<td>1.17</td>
<td>0.66</td>
<td>0.92</td>
</tr>
<tr>
<td>11</td>
<td>1.09</td>
<td>0.55</td>
<td>0.91</td>
</tr>
<tr>
<td>12</td>
<td>0.78</td>
<td>0.34</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean values</td>
<td>1.15</td>
<td>0.58</td>
<td>0.92</td>
</tr>
</tbody>
</table>

One should also note the difference in the image acquisition process between the two settings. In the axial set the images are collected by moving the probe cranial to caudal, resulting in a variation of the contact between the probe and the gland. This contact may result in small vertical movements of the prostate between different slices and affect the reconstructed models, where one has assumed that all the slices were acquired without movement of the gland. In the other hand, the longitudinal set is acquired by rotating the US array along its own axis, while keeping it still in relation to translation, and therefore are less likely to induce movement of the gland during the process. With the objective of verifying if this movement was in fact relevant one has compared the two sets in a side view as can be seen in Figures 4.8 for two of the patients. However, besides some differences in the profiles, there wasn’t any evidence of significant movement in the axial acquisition.

4.2.3 Registration

In this section one will present the results of applying the registration algorithm described in chapter 3 to the brachytherapy data.
4.2.3.A Evaluation Methods

For the evaluation of the registration results, one will use the same metrics introduced in subsection 4.2.2.A, the MAD using P2P and P2S and the DSC.

4.2.3.B Experimental data

In table 4.5 one may find the values of the three error metrics already explained for each case of the data set in three different moments of the registration process. The first is after aligning the US points and the MRI surface by the centers of mass, which is the initial position for the rigid registration. Then these values are again calculated after that registration and finally the MAD and DSC are calculated after the elastic registration that is the last step of the process. The mean values for all the cases are shown in the last row of the table and can also be visualized in the bar graphs in Figure 4.9.

By analysing the results one may verify that after aligning the center of mass for the initial guess of the registration one can already induce a good match between the two modalities, with a MAD P2S of 0.51 mm and a DSC of 90.8%. These values are then slightly improved with the rigid registration until a MAD P2S of 0.47 mm and a DSC of 91.5%. At this point the difference between the two surfaces is mainly due to different deformation states and no further iterations can improve this value. The elastic deformation step is then applied, resulting in a reduction of the MAD errors to approximately half and increasing the DSC to 96.7%, a value very close to the perfect match.

These values can be compared to the study performed by Makni et al. [64] where a similar method has been applied but using a smaller number of landmarks for the elastic warping. The values obtained in that article were a MAD of 1.09 mm and a DSC of 89% for the prostate boundary. The values obtained in this work appear to present a better performance. Nevertheless, the MAD and DSC were computed based on the surface points that were used in the registration process and for calculating the elastic warping and thus can’t provide an independent measurement quantifying the performance. In order to provide a good quantification, one would require good features/landmarks inside the prostate. Unfortunately the gland does not have good features beside the boundary that can be identified in both MRI and US modalities, and the urethra that is sometimes used for that purpose is poorly identifiable in the MRI without a catheter.
Table 4.5: Results of the MRI/TRUS fusion showing the evolution of the MAD errors using point to point (P2P) and point to surface (P2S) and the DSC along the registration process, after aligning the centers of mass (CM), the rigid registration and the elastic registration.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial with CM aligned</th>
<th>After rigid registration</th>
<th>After elastic registration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P2P(mm)</td>
<td>P2S(mm)</td>
<td>DSC</td>
</tr>
<tr>
<td>1</td>
<td>1.414</td>
<td>0.510</td>
<td>0.881</td>
</tr>
<tr>
<td>2</td>
<td>1.503</td>
<td>0.637</td>
<td>0.897</td>
</tr>
<tr>
<td>3</td>
<td>1.521</td>
<td>0.653</td>
<td>0.894</td>
</tr>
<tr>
<td>4</td>
<td>1.358</td>
<td>0.491</td>
<td>0.897</td>
</tr>
<tr>
<td>5</td>
<td>1.126</td>
<td>0.444</td>
<td>0.928</td>
</tr>
<tr>
<td>6</td>
<td>1.572</td>
<td>0.666</td>
<td>0.884</td>
</tr>
<tr>
<td>7</td>
<td>1.150</td>
<td>0.469</td>
<td>0.915</td>
</tr>
<tr>
<td>8</td>
<td>1.073</td>
<td>0.443</td>
<td>0.939</td>
</tr>
<tr>
<td>9</td>
<td>1.124</td>
<td>0.474</td>
<td>0.917</td>
</tr>
<tr>
<td>10</td>
<td>1.284</td>
<td>0.563</td>
<td>0.920</td>
</tr>
<tr>
<td>11</td>
<td>0.919</td>
<td>0.329</td>
<td>0.922</td>
</tr>
<tr>
<td>12</td>
<td>1.158</td>
<td>0.435</td>
<td>0.904</td>
</tr>
</tbody>
</table>

Mean ± Std. 1.267±0.198 0.510±0.097 0.908±0.018 1.189±0.240 0.472±0.116 0.915±0.022 0.578±0.229 0.194±0.125 0.967±0.020
Figure 4.9: Evolution of the MAD using point to point a) and point to surface b) approaches and DSC values c) along the different steps of the registration process.
4.3 Discussion

Although the US image acquisition was performed only at the beginning of the intervention, the prostate may suffer deformation and other effects that may introduce some errors in this procedure. This deformation is caused not only by moving the transducer inside the rectum, but also by the insertion of the needles. Furthermore, the gland may suffer edema caused by the injury of small internal vessels and the consequent hemorrhage that leads to volume changes in the prostate. Therefore, in order to optimize error in the procedure, one could minimize the effect caused by moving the probe inside the rectum by creating a 3-D transducer that would acquire the whole volume without any movement. An example of systems proposed in the literature to solve this issue are the Koelis Urostation [85] and TargetScan [86], where the transducer array is moved inside a fixed cap with a motorized system. The implementation of such a system would also enable a real-time acquisition without requiring a manual and extensive procedure as the one currently performed. By performing real-time acquisition one could account for the deformations and adapt the registration.

The objective of the system proposed here is to enable a focal brachytherapy procedure, placing radioactive seeds only in areas with high probability of presenting cancerous tissue. This tool takes advantage of the high predictive value for PCa provided by the multiparametric MRI images as well as the high availability of the US systems. Using this software, the medical team identifies the cancer lesions in the MR images. Then, during the procedure, after the registration process is completed, the resultant deformation map is applied, as in Figure 3.5(d), to locate those lesions in the US images, as illustrated in Figure 1.7. The insertion of the seeds would then be performed as in the current procedure, but focusing on the lesion sites. Based on the results obtained in this work, the registration error committed during this process is estimated to be below 1 mm near the boundaries of the prostate. As for the error committed in the inner part of the gland, further studies have to be performed in order to quantify that value. However, according to a similar study performed by Makni et al. [64], which achieved lower results than ours in the boundary region, the highest registration error was found in the urethra-bladder interface with values ranging from 2 to 3 mm.

One should notice that the method described here is not only applicable to the brachytherapy intervention. Since it is used for needle navigation in the MRI volume, it may be adapted for any other intervention intended for transperineal approach. Therefore, instead of introducing the radioactive seeds in the prostate, one may introduce biopsy needles for the sampling of suspicious lesions found in MRI and then save the position for later therapy. It can also present a solution for focal therapy. As has been discussed in the introductory chapter, transperineal approach is not expected to be the adopted solution for the millions of biopsies that are performed every year because of the need for anaesthesia and the costs it involves. However, it may become a robust solution for repeated biopsies and focal therapy.
Applications: Biopsy
In this chapter, a study is presented for the transrectal biopsy exam. The structure of the chapter is analogous to the one used in preceding one for brachytherapy, starting with a description of materials and methods, then the results and the discussion.

Although the overall issue of this work was MRI/TRUS registration, the study presented in this chapter does not contain the MRI part. This is due to nowadays, TRUS guided biopsies are the first diagnostic exam to be performed after PCa suspicion in PSA or DRE, and normal patients attending prostate biopsies do not perform a prior MRI. Therefore, the study presented in this chapter will focus mainly on the location of the biopsy cores inside a 3-D US volume.

5.1 Materials and Methods

5.1.1 Experiments

The experimental data presented in this chapter has been obtained during 22 transrectal biopsy exams performed in Hospital Curry Cabral during three different sessions in July of 2012. The exams were performed by Dr. Miguel Almeida, a member of the medical team of Dr. Jorge Fonseca. All the data has been recorded anonymously.

During the procedure, all the patients underwent local anaesthesia by injecting a mean volume of 6 mL of anaesthetic in the space between the rectum wall and the prostate. The cores were then collected with a biopsy gun using a sextant approach with the help of a free-hand US scanner, where 2 or 3 cores were taken from the base, midgland and apex, lateral directed to both right and left side of the gland, resulting in 6 different zones with 2 or 3 fragments each.

5.1.2 Tracking system

In order to record the position of the US probe during the procedure, a Polaris Spectra® optical tracking system commercialized by NDI was used. The optical tracker was fixed to the probe using a tool constructed for the purpose as shown in Figure 5.2(a). The infrared camera that tracks the tool was positioned right in front of the patient with a tripod in order to get an upside view from the tracker, as can be seen in Figure 5.2(b), and therefore be able to record every position of the probe. Using the system, each frame collected during the procedure was spatially localized inside the operating room.

![Figure 5.1: Polaris Spectra® cameras used to track the US probe, image from NDI (www.ndigital.com).](image-url)
Figure 5.2: Probe with the optical reflectors installed a) and the acquisition process during the biopsy procedure b).

5.1.3 TRUS images

The TRUS images were obtained using a Mindray M5 US system and an endfire transducer, model 6cv1s. The images were recorded by the computer using a framegrabber model Grabby commercialized by Terratec connected to the S-video output of the US system with a frame rate of 25 frames per second.

During the first two biopsy sessions (first 14 patients), a 3-D volume of the prostate was acquired at the beginning of the procedure and before the anaesthesia, by performing a free-hand sweep that enabled the visualization of the whole organ. At the time of each biopsy a set of ultrasound images were recorded together with probe position in order to determine the corresponding location in the world frame. In the last of the three biopsy sessions, the prostate sweep was repeated after the anaesthesia, at the middle of the procedure and at the end, in order to study the motion of the gland during the whole procedure.

The images were later segmented using the manual tools implemented and the points were then transformed according to the transformation acquired by the tracker in order to create the cloud point to be interpolated by the RBF. In Figure 5.3 one may observe the US images positioned according to the transformation given by the tracking tool. The points acquired with the segmentation of each frame are also displayed with red points and the resulting 3-D model is also shown in brown.

As one can see, since the images were obtained with free-hand motion of the probe, the frames are not as regularly distributed as in Figure 4.2(b) where the probe was moved with the help of the stepper.
5.1.4 Calibration of US images and tracker acquisition.

In order to perform a good reconstruction one needs to synchronize the US images and tracker position in a calibration process. This step was not required when acquiring the brachytherapy images since the images were acquired with small and slow motions of the probe. Still, free-hand acquisition is a dynamic process where the time is an important constraint since a few fractions of second may result in very different positions.

As regards to the US images, since they are acquired using ultrasound waves that travel to the human tissue, are pre-processed in the US system and then later sampled using the framegrabber at 25 frames per second, the images acquired by the computer will be delayed in relation to the real-time ones. On the other hand, the tracker position is also acquired at 25 Hz (reads per second) but it is almost real-time with very small delays in the process.

To identify the delay between the two images, instead of acquiring the prostate volume with a free hand sweep in one direction, a second sweep was performed in the opposite direction. In this way, one could compare the images from the two sweeps in order to check if they matched each other or if they were shifted in space. After segmenting the sets for the two sweeps these were positioned according to the positions acquired with the tracker at the same time and compared them to the ones resultant of introducing different time delays. The time delay considered to be the real one was the one that produced reconstructed volumes where both sweeps matched. Figure 5.4 displays the difference between the original reconstructions without time shift and the ones reconstructed with chosen correct delay. As one can easily observe, in figure 5.4(a) the two models are not consistent with each other. In the other hand, after correcting the delay the models are correctly matched. After
producing these images for different patients, one has observed that the offset that best synchronized the US images and the tracker positions was 3 frames, which at 25 Hz corresponds to 0.12 s.

This delay is inside the expected interval, as the final delay of the US image is the sum of the sampling frequency of the US array, that was set to be 14 Hz (resulting in 0.07 ms for each frame) and the time taken for the framegrabber to convert the image at 25 Hz (resulting in 0.04 ms).

The time delay of 0.12 ms was used to calibrate the US image and tracker position in all the experiments performed in this chapter.

![Figure 5.4](image)  
**Figure 5.4:** Reconstruction based on the images and tracker position without time shift a) and with a time shift of 0.12 s b). The blue surface is the result using the first sweep and in brown is the sweep in the opposite direction.

### 5.1.5 Biopsy cores collection.

As already explained, during the biopsy exams the biopsy gun is oriented with the help of an endfire US probe and, when the desired position is reached, the biopsy needle is fired in order to collect a core.

For locating the position of the cores, the US images are recorded at the time of each biopsy shot, and then analysed in order to locate the needle in the image plane. The position is later combined with the tracker information in order to display the biopsy core inside the prostate volume. For easier comprehension of the core location, one has also segmented the contour of the prostate in the US image at the time of the shot, as will be seen in the results section. This segmented contour will be useful to see the position of the prostate relative to the initial position.

In Figure 5.5(a) one may see a photo of the needle tip showing the place where the 2 cm core is collected. In Figure 5.5(b) an US image is displayed at the time of the biopsy acquisition, showing the expected needle path (white dots) and the real needle trajectory with a superimposed blue line. This line is part of the developed tool and is positioned by the user in order to locate the needle in the image plane.
5.2 Results

In this section one will present the results of studying the biopsy procedure. As was explained before, there were some differences between the image acquisition in the first two sessions and the third. The results obtained in the first two sessions, where the prostate volume was acquired only at the beginning of the exam will be presented first. Then, the results obtained during the third session where several volumes were acquired throughout the exam will be shown, in order to make a quantitative evaluation of the gland movement during the procedure.

In the first two sessions, the images of the prostate were segmented in its initial position before the anaesthesia. Then the images acquired at the time of the biopsy shots were analysed as discussed in subsection 5.1.5 resulting in acquiring the core location and the contour of the prostate at that moment. The result of this analysis for four of the patients may be visualized in Figure 5.6 where the model of the prostate in the initial position is shown along with the segmented contours in red and biopsy cores displayed as cylinders.

As one can observe, the segmented contours are very far from the initially acquired prostate volume as well as the biopsy cores, that appear very far from the initial position. The results in Figures 5.6(a) and 5.6(b) are the ones that present the biggest displacement of the gland between initial position and the moment of collection of the cores, resulting in cores that are all pushed inside the prostate and some even perforating the surface of the prostate more distal to the rectum. In the other hand, Figures 5.6(c) and 5.6(d) present a smaller displacement of the gland causing the biopsy cores to be closer to the initial position but still displacement is notorious, from the position of the red contours.

Another observation that can be taken from these results and is evident in Figure 5.6(c) is that the position of the prostate is not only different from the initial position to the time of collection of the cores, but also between the acquisition of each core. Being so, although one can slightly improve the location of the cores by creating a cloud with all the red contours and register it in the initial surface with ICP, it would still be far from the correct location. Another solution to better locate the cores would be to use
the ICP to register the red contour of each core independently in the initial surface. However, it would still be very inaccurate because using the segmentation of only one plane wouldn’t provide a robust registration as different sections may have very similar profiles, for example, individual contours in both right and left side may seem very similar but they are in opposite sites of the gland.

![Image](image_url)

**Figure 5.6:** Images showing the results of different biopsy exams. In brown is the prostate model based on the images acquired at the beginning of the procedure. The red points represent segmentation of images acquired at the time of each biopsy core acquisition. The biopsy cores location are also displayed in the image.

After analysing the data of these first sessions, one has concluded that the movements of the prostate during the procedure were quite significant and that using only the information collected in those sessions it would be impossible to correctly locate the cores inside the prostate. In order to quantify the displacement of the gland during the exam the acquisition methodology was modified in the last session. Instead of acquiring the US prostate volume only at the beginning of the proce-
dure, as before, the volume acquisition was repeated after the anaesthesia, at the middle of the core collection, i.e. after half of the biopsy cores being collected, and finally at the end of the procedure. Although the ideal solution would be to obtain the US volume at the time of each biopsy in order to be able to register the images of the gland with the ones in the initial position, that would interfere with the normal procedure and therefore was not used.

For analysing the data of this session, the prostate volume was reconstructed, with the same method already described, at the four time instances of the procedure. Then, the latter three were registered in the initial reconstruction using the rigid registration algorithm and the displacement was computed as the norm of the translation vector. The results obtained are displayed in Table 5.1. In patients 2 and 6 there is no value for the end of the procedure because the final sweep was not performed. For computing the mean value and in the rest of the analysis, one has excluded patients 3 and 6 as their displacements are very discrepant from the others and probably due to the movement of the patient and not only the prostate.

Table 5.1: Displacement of the prostate in mm relative to the initial position during the biopsy exam, at three different moments: after the anaesthesia, at the middle of the procedures and after all the biopsy cores being collected. The mean value was calculated without the patient 3 and 6 as the values are discrepant form the others.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Displacement in mm relative to initial position</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After anaesthesia</td>
<td>Middle of procedure</td>
</tr>
<tr>
<td>1</td>
<td>1.79</td>
<td>12.60</td>
</tr>
<tr>
<td>2</td>
<td>2.35</td>
<td>6.91</td>
</tr>
<tr>
<td>3</td>
<td>11.99</td>
<td>25.20</td>
</tr>
<tr>
<td>4</td>
<td>1.74</td>
<td>13.50</td>
</tr>
<tr>
<td>5</td>
<td>7.89</td>
<td>10.95</td>
</tr>
<tr>
<td>6</td>
<td>24.05</td>
<td>40.20</td>
</tr>
<tr>
<td>7</td>
<td>5.37</td>
<td>16.00</td>
</tr>
<tr>
<td>8</td>
<td>4.42</td>
<td>11.37</td>
</tr>
<tr>
<td>Mean value (e. 3 and 6)</td>
<td>3.93</td>
<td>11.89</td>
</tr>
</tbody>
</table>

In the first column of the table, one may analyse the effect of injecting the 6 cm$^3$ of anaesthetic between the rectum wall and the gland. Comparing this volume to the mean size of the prostate that according to [87] is between 24 cm$^3$ at age of 50-54 years and 38 cm$^3$ above 75 years, one may conclude that it is very significant. As seen in the table, this injection results in a mean displacement of approximately 4 mm. Halfway through the procedure the mean displacement is 12mm, and at the end of the procedure the displacement is 18mm.

5.3 Discussion

The initial displacement of the prostate after the injection of the anaesthesia is mainly due to the volume of liquid inserted. The first and second sweep scans are performed with little force being applied on the prostate by the probe. For the third and fourth sweep scans, the displacements are much larger, and that is due to the combination of two factors: first due to the contact between the probe and the gland, since at the time of the biopsy shot it is necessary to push the probe against the surface of the prostate which induces deformation and translation; second by the movement of
the patient as a reaction to discomfort and pain. Since one has only monitored the probe and not the
patient, one cannot dissociate the two types of movement, being the final displacement a combination
of the two factors. Nevertheless, no significant motion of most of the patients was visually observed
during the procedure.

Analysing these values, one can quantitatively explain the results obtained in the first two sessions
where it was observed that an initial sweep wasn’t enough to register the biopsy cores inside the
prostate. In fact, even performing more acquiring steps, as was done in the last session, it is still not
enough since the difference between two consequent sweeps is in the order of 6 mm.

Based on the results obtained during this biopsy procedures, one has identified that in order to
achieve good results at registering the biopsy cores inside the prostate, one should acquire the whole
US volume at the time of collecting each core. However, performing the acquisition free-hand is
a time consuming process that interferes in the normal procedure. Furthermore, during this work
one has assumed that there wasn’t any deformation of the prostate during the sweep to acquire the
3-D volume and the final reconstructed shape of the gland was based in different frames collected
while varying the probes position. In fact, its not necessarily the case since the probe is free-hand
driven and different pressures may be applied along the sweep. With the objective of improving this
drawbacks, one should use a probe like the one proposed in Baumann et al. [36] where a motorized
2-D endfire array is used to sweep the whole volume and acquire the 3-D volume. Figure 5.7 taken
from [36] explains the 3D image acquisition from an oscillating 2D US sensor head.

![Figure 5.7](image)

**Figure 5.7:** Schematic illustration of the 3-D biopsy probe proposed by Baumann et al. (image taken from [36]). The 2-D endfire image a), the motorized sweep plane b) and the final 3-D volume c).

The most important contribution of the study presented in this chapter was to uncover and quantify
the prostate motion during the biopsy procedure. This fact presents a large obstacle to correctly
localize the biopsy samples inside the gland and, therefore, the ability to perform targeted biopsies.
On one hand, this reveals the necessity of a strategy to control the pressure that the probe exerts
again the prostate, which can nowadays be performed accurately with the help of robotic systems.
One the other hand, it uncovers the importance of real-time 3D volume reconstruction tools to achieve
a correct prostate location. Therefore, these two approaches are a path to follow in future work.

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## Conclusions and Future Work

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6.1 Conclusions

The presented work focused on developing an elastic registration methodology between MR and TRUS images, to be used both in the diagnostic and focal treatment of PCa, the most common cancer in men and with a tendency to increase in the upcoming years as the world population ages. This multi-modality approach has the advantage of providing additional invaluable information that cannot be granted with single-modality approaches, enabling a better location and characterization of the cancerous tissue while keeping it cost-effective. Although the study herein presented has been specially focused in the brachytherapy procedure, the approach was designed to be general enough to be further extended to other prostate procedures.

The first main improvement implemented in the brachytherapy procedure was a semi-automatic prostate segmentation of the axial TRUS images. This tool has the advantage of enabling a faster and simpler execution of the procedure while still keeping the medical team in control. In order to do so, an Active Shape Models (ASM) approach was used, where a Statistical Shape Model (SSM) was built to provide a powerful prior estimation of the prostate shape that was later optimized according to an energy minimization search. The clinician is then provided with an editing tool in order to verify the segmentation and improve it according to his medical knowledge. In order to improve the performance of this tool, one has tested a prior filtering of the US images for noise removal. However the small increment in performance was not enough to justify the expensive computational time required. The algorithm applied to the US images yielded good results in fully automatic mode, with a MAD of approximately 2 mm and a DSC of 90%, similar to the ones found in the literature. Furthermore, the performance of the tool was best in the midgland region, where these values improved to a MAD of 1.6 mm and a DSC of 94%. As for the base and apex region, the results were not as good due to lower contrast and less definite borders. Nevertheless, these regions are also the harder for the clinicians to identify manually and therefore the ground truth is less robust.

As for the registration algorithm, one has implemented a robust tool that was successful to find the match between the prostate images found in the US dataset and the ones collected with the MRI. This registration combines a rigid body movement with an elastic deformation, and allows the correspondence between points in the US and the MRI reference frames. The big improvement that this registration brings to the brachytherapy is the possibility to overlay on the TRUS images the location of the lesions only visible in multiparametric MRI, thus allowing the visualization of their relative position to the radioactive seeds, as well as the possibility of performing focal therapies. The results obtained with the proposed system after the registration process resulted in a MAD between the US mesh points and the MRI surface of approximately 0.2 mm and a DSC between the two volumes of 0.97%. These values show that the outer limits of the prostate in the two image modalities are very similar. However, due to the lack of image features inside the gland that are visible in both modalities, one can only interpolate the error in that region based on the errors of the boundaries.

One should notice that, in this study, the registration was applied to the images acquired at the beginning of the procedure. However, the prostate may suffer deformation caused not only by moving...
the transducer inside the rectum, but also by the insertion of the needles. Furthermore, the gland may suffer edema caused by the injury of small internal vessels and the consequent haemorrhage that leads to volume changes in the prostate. Therefore, in order to optimize error in the procedure, one could minimize the effect caused by moving the probe inside the rectum by using a 3-D transducer that would not only acquire the whole volume without any movement but also be able to automatically collect new volumes throughout the procedure without requiring the time consuming manual acquisition. In this way, the registration would be repeated along the intervention enabling the correction of the deformation and edema that would happen during the procedure, thus keeping the elastic registration in real time.

Finally, a preliminary study of the prostate biopsy exam has been performed in order to test the extensibility of the proposed registration method to this procedure as well as the study of the gland movement during the exam and the location of the biopsy cores in the US volume. However, one could not meet the first objective because MRI data was not available at the time of the biopsies, as currently it is not part of the standard diagnostic procedure. Therefore, this part of the work will have to be incorporated in a forthcoming study. In what concerns the movement of the gland during the exam, the results of this study showed that there are very large displacements of the gland during the procedure, as the mean displacement, for the patients studied, from the beginning to the end of the procedure was almost 18 mm. This value was mainly due to the injection of the anaesthetic, the pressure caused by the probe and the movement of the patient as a reaction to pain/discomfort. Therefore, and since the data was being acquired by a 2D transducer coupled to a tracking sensor, this order of movement compromised the robust location of the cores using a volume acquired in a different instant of time.

The study presented in this work is an important contribution for the current trends in the PCa management, both in the diagnosis, through active surveillance, and in the treatment, with focal therapy. The advantages introduced by these techniques not only benefit the patients, as these more conservative therapies improve their quality of life and reduce morbidity effects caused by radical therapies, but also the healthcare systems, as those radical therapies are normally much more expensive than the ones proposed.

6.2 Future work

The future work proposed is twofold. For the brachytherapy procedure, as already has been discussed, a future study should include the implementation of a 3D US transducer. This tool should be capable of automatically acquiring the whole volume without the necessity of moving the US probe during the procedure and the ability to collect new volumes throughout the procedure without requiring manual intervention. Such a system would enable the extension of the present software to real-time. Furthermore, a posterior study should be developed using phantom models of the prostate with visible features to better quantify the registration error.

With respect to the biopsy, future work should also adopt 3D transducers, as already proposed
by some authors, to acquire the whole volume at the time the biopsy needle is fired, in order to be then registered in an initial reference frame. That work would also take advantage of the extension of the semi-automatic segmentation tool designed above to the acquisition methodology used in free-hand biopsy, thus enabling a faster analysis of the exam data. Furthermore, in order to test the extension of the registration software to the biopsy procedure, one could start a study where some patients undergoing this exam would perform a prior MRI, to be used for localizing lesions, and the consequent biopsy cores.

Finally, another major improvement to the current biopsy procedure would be the implementation of a robotic system to manipulate the probe. With the help of such a system, the exerted force can be better controlled and higher targeting position can be achieved.
Bibliography


[87] R. Berges and M. Oelke, “Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling
A

Fusion images sets
In the following Figures A.1 and A.2 one may find two example sets of fusion images after the elastic registration. The MR image is shown in upper left and bottom right, the US image in upper right and bottom left and the contour obtained from the US segmentation is superimposed in blue.

**Figure A.1:** Set of fusion images obtained after the elastic registration for patient 4.
Figure A.2: Set of fusion images obtained after the elastic registration for patient 11.