TOMOSYNTHESIS-BASED INTRAOPERATIVE DOSIMETRY FOR LOW DOSE RATE PROSTATE BRACHYTHERAPY

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ABSTRACT

The aim of this study is to develop an intraoperative dose assessment procedure that can be performed after an I-125 prostate seed implantation, while the patient is still under anaesthesia. To accomplish this, we reconstruct the 3D position of each seed and co-register it with the prostate contour acquired with a transrectal ultrasound (TRUS) probe. Our seed detection method involves a tomosynthesis-based filtered reconstruction of the volume of interest requiring 7 projections acquired over an angle of 60° with an isocentric imaging system. The co-registration between the tomosynthesis-based seed positions and the TRUS-based prostate contour is based on the planned position. A phantom and a clinical study (25 patients) were carried out to validate the technique. In the patient study, the automatic tomosynthesis-based reconstruction yields a seed detection rate of 96.7% and less than 2.6% false-positive. The seed localization error obtained with a phantom study is 0.4 ± 0.4 mm. The co-registration method based on planned seed position has proved to be not accurate enough for dosimetric purposes. We believe that this technique may be used to discover considerable underdosage and to improve the dosimetric coverage by potentially reimplanting additional seeds.
L’objectif de ce projet est de développer une procédure d’évaluation dosimétrique intra-opératoire en implantation prostatique de grains d’iode 125. Pour y arriver, la position 3D des grains doit être reconstruite et recalée avec les contours de la prostate imagée en échographie endorectale. La reconstruction des grains est basée sur une technique de tomosynthèse requérant 7 projections acquises entre -30° et 30°. Le recalage entre la position 3D des grains et les contours utilise comme cible la position planifiée des grains. Notre technique de reconstruction dosimétrique a été testée sur un mannequin et dans une étude clinique incluant 25 patients. Notre méthode permet de reconstruire la position 3D des grains avec une précision de 0.4 ± 0.4 mm. De plus, l’étude clinique a démontré un taux de détection de 96.7% des grains et incluant moins de 2.6% de faux-positifs. La méthode de recalage n’a pas permis d’atteindre une précision acceptable pour une application clinique. La technique développée permet de repérer la présence de sous-dosage considérable et ouvre la porte vers la réimplantation de grains additionnels afin d’améliorer la couverture dosimétrique de la prostate.
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Chapter 1
Introduction

Nowadays, prostate cancer is the leading type of cancer among Canadian men. In 2008, it is estimated that 24700 new cases will be diagnosed, accounting for 28.4% of the new cancer cases [1]. Even with a very favourable 95% five-year relative survival ratio, prostate cancer is still the third leading cause of cancer death in men, causing approximately 4300 deceases in 2008 in Canada. An increasing fraction of those cancers are detected in early stages with the extensive screening program developed in the 90s, based on prostate-specific antigen (PSA) testing and digital rectal examination. Because prostate cancer is often slow-growing, a program of watchful waiting is commonly recommended when the risks of intervention or therapy may outweigh the benefits. However, when a treatment is recommended, several options are available, the most common being listed below:

- Surgical removal of the prostate (prostatectomy),
- External beam radiation (EBRT),
- Low dose rate (LDR) brachytherapy,
- High dose rate (HDR) brachytherapy,
- Hormonal therapy,
- Chemotherapy,
- Or combination of these treatments.
1.1 LDR prostate brachytherapy

Prostate brachytherapy was one of the first applications of ionizing radiation to treat a form of cancer. Indeed, as a first attempt, Pasteau and Delgrais used radium inserted through a urethral catheter in 1914 in Paris [2]. However, brachytherapy has not been a viable treatment option for prostate cancer before the introduction of the transrectal ultrasound (TRUS) probe in the late 80s, which allowed real-time guidance during the implantation. The recent technological advances in imaging, delivery apparatus and treatment planning led to a renewed interest in permanent seed implant. Nowadays, it is estimated that 30% to 40% of all eligible patients with prostate cancer receive LDR brachytherapy as part of their treatment in the United States [3]. This is approximately a 15-fold increase compared to new cases that were treated with permanent implant in 1995.

In LDR prostate brachytherapy, small encapsulated seeds of low-energy radioactive materials, generally I-125 or Pd-103, are implanted permanently into the prostate. These seeds slowly release their radioactivity to deliver a dose of radiation to the cancerous tissue of the prostate. This interstitial brachytherapy treatment allows a maximum dose delivery to the target volume while sparing surrounding tissue, because of the rapid dose fall-off outside of the prostate boundary. Clinical results suggest that this treatment alone is suitable for patient with localized prostate cancer, grade T1 to T2a, with PSA level < 10 ng/ml and with Gleason score \( \leq 6 \) [4]. Furthermore, glands larger than 60 cc may cause technical difficulties to implant due to pubic arch interference and because of the large number of seeds required.
Most of the studies suggest that prostate brachytherapy offers a PSA-based control rate comparable with prostatectomy or external beam radiation [5, 6]. The main advantages of seed implant over these treatments are lower morbidity rates and reduced urinary or rectal complication and sexual dysfunction [7]. Besides, the operation is a one day procedure, performed as an outpatient procedure, and the patient can usually return to his normal activities within a week.

1.2 Problem description & specific aims of this study

As in any other treatment using ionizing radiation to treat cancer, the clinical outcome is dependent on the quality of the dosimetric coverage of the target. The minimum dose delivered to 90% of the prostate volume, $D_{90}$, and the percentage of prostate volume that received a dose equal to or greater than the prescribed dose, $V_{100}$, are commonly considered as the most important dosimetric quantifiers [8, 9].

Following the implantation procedure, the clinical team has very limited information to know how well the real implant matches the treatment plan. This can be problematic since small deviations from the treatment plan can cause major flaws in the dosimetric coverage. Indeed, the short range of the photons emitted by the low-energy radioactive sources can lead to undesirable cold spots in the target volume. The development of a postimplant intraoperative dosimetry procedure would allow the identification of significant underdosed regions while the patient is still under anaesthesia in the operating room (OR). To accomplish this, we need to reconstruct the 3D position of each seed and co-register it with the prostate contour. This has to be done with minimum additional time to the procedure and with the imaging modalities commonly available in the OR. With this information in hand, the clinical
team could decide to improve the dosimetric coverage by potentially reimplanting additional seeds. Thus the two specific aims of this project are:

1. Reconstruction of the 3D position of the implanted seeds using plane radiographs,

2. Co-registration of the seed position with the boundary of the prostate acquired with TRUS imaging.

1.3 Overview of the thesis structure

This thesis is divided into 8 chapters, including the introduction and the conclusion. Chapter 2 describes the prostate implantation procedure, the dose calculation formalism in brachytherapy and a review of literature of the postimplant dose evaluation procedure. The various image processing steps to format the plane radiographs into the proper format for the seed position reconstruction algorithm are detailed in chapter 3. The tomosynthesis-based algorithm using these images to reconstruct the seed positions is presented in chapter 4. Furthermore, the same chapter includes the validation of the seed position reconstruction on a phantom and a clinical study. Chapter 5 describes the method to co-register the prostate contours with the seed positions. The evolution of the dosimetric information for the patient study is presented in chapter 6. Finally, chapter 7 presents an overview of the graphical user interface allowing the user to get visual feedback of all the steps leading to the intraoperative dosimetry information.
Chapter 2
LDR Prostate Brachytherapy: Procedure and Dosimetry

2.1 Implantation procedure

The clinical procedure summarized in this section reports to the technique of seed implant at the Hôpital Notre-Dame of the Centre Hospitalier de l’Université de Montréal (CHUM). The entire operation, from anesthesia to the end of the implantation, takes an average of 90 to 120 minutes. During the implantation, the patient is under anesthesia, in lithotomical position. The characteristics of the implanted radioactive isotopes (selectSeed\textsuperscript{TM}, Nucletron) are presented in table 2–1. With an half-life of 59.4 days, approximately 90% of the dose is delivered over the first 6 month interval. The whole clinical procedure, using the Nucletron FIRST System, can be divided into 3 principal steps:

1. Prostate volume study,
2. Intraoperative treatment planning,
3. Implantation of the I-125 sources.

Table 2–1: Characteristics of the iodine-125 radioisotope

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Size (diameter × length)</th>
<th>Half-life</th>
<th>Average energy</th>
<th>Half-value layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-125</td>
<td>0.8 mm × 4.5 mm</td>
<td>59.4 days</td>
<td>28 keV</td>
<td>2 cm of tissue</td>
</tr>
</tbody>
</table>

5
Prostate volume study. The first step is to determine the shape and the position of the patient’s prostate. This is performed with the TRUS probe which provides good soft tissue contrast. The volumetric study is done by contouring the prostate, the urethra and the rectum wall on successive axial TRUS images acquired with a 2.5 mm slice thickness. Then, this information is feed into the SPOT PRO™, a mobile 3D planning system, to generate the treatment planning.

Intraoperative inverse treatment planning. The aim of the treatment planning is to provide the number of seeds to implant and their optimized positions relatively to the prostate contours. Compared to pre-planning, where all calculations are made well ahead the date of treatment, intraoperative planning can provide significantly better dosimetric parameters [10]. An inverse planning simulated annealing (IPSA) algorithm is used to achieve an optimized 3D dose distribution [11]. The plan is generated to deliver a uniform dose of 144 Gy to the prostate plus a 2 mm margin while minimizing the exposure to the organs-at-risk (OAR), the urethra.

Figure 2–1: Comparison of an I-125 seed with a dime. Figure taken from Centre hospitalier universitaire de Québec (CHUQ) patient’s guide.
and the rectum wall. Table 2–2 presents in details the different dosimetric aims for the target and OAR. The seeds are preferentially implanted at the periphery of the prostate to minimize the dose given to the urethra located near the center of the target.

Table 2–2: Specific aims of the intraoperative plan in terms of dosimetric parameters.

<table>
<thead>
<tr>
<th></th>
<th>Prostate</th>
<th>Urethra</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{100}$ $&gt;$ 98%</td>
<td>$D_2$ $&lt;$ 220 Gy</td>
<td>$V_{100}$ $&gt;$ 2 cc</td>
<td></td>
</tr>
<tr>
<td>$V_{150}$ $&gt;$ 62%</td>
<td>$D_5$ $&lt;$ 200 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{90}$ $&gt;$ 175 Gy</td>
<td>$V_{150}$ $=$ 0 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Implantation of the I-125 sources.** Once the treatment plan is generated, loose seeds are deposited in the planned position through transperineal needles implanted in the region between the scrotum and anus, the perineum (figure 2–2). For the 25 patients that were analyzed in this study, an average of 52 radioactive I-125 sources (min: 36 and max: 69) were implanted into the prostate. Bio-compatible plastic spacers, with dimensions similar to a single seed, are disposed between the seeds to adjust the interseed distance in the needle axis and to reduce seed movement along the needle axis.

The placement of needles is guided with a template and TRUS imaging. Once a needle is well positioned, seeds are automatically handled and placed in the needle by the seedSelectron® system, an automated seed delivery device part of the Nucletron FIRST System. If the needle positioning, visible on the TRUS, deviates
Figure 2–2: Schematic representation of the TRUS guided implantation. This figure presents the TRUS probe, a transperineal needle and the brachytherapy template.

from the planned position, the physicist can specify manually the actual needle positioning in the treatment planning software. These corrections allow to compute an updated planned dosimetry, accounting for real needle placement. The retraction of the needles is performed manually by the physician.

2.2 TG-43 dosimetry formalism

The current standards for dose calculation in brachytherapy are provided by the report of the Task Group No. 43 (TG-43) published in 1995 by the American Association of Physicists in Medicine (AAPM) [12]. An update to this report was published in 2004 [13] to include new source models and to modify some aspects of the original TG-43 dosimetry formalism. All the dosimetric calculations in this study are done with the ”old” 1D formalism, which uses the isotropic point-source approximation. In this study, the main reason to use the 1D formalism is to be consistent with SPOT PRO\textsuperscript{TM} the treatment planning system that uses the same approximation at our institution. Furthermore, the 1D formalism simplifies the
source localization procedure by eliminating the need to reconstruct the orientation of each seed. However, SPOT PRO\textsuperscript{TM} does support the 2D line source approximation. The dose rate $\dot{D}$ of a single seed with the point source approximation formalism is calculated with the following equation:

$$\dot{D}(r) = S_K \cdot \Lambda \cdot \left( \frac{r_0}{r} \right)^2 \cdot g_P(r) \cdot \phi_{an}(r).$$ (2.1)

where $r$ denotes the distance between the center of the source and the point-of-interest, $r_0$ denotes the reference 1 cm distance, $\theta$ represents the polar angle specifying the point-of-interest, $S_K$ is the air-kerma strength, $\Lambda$ is the dose-rate constant, $g_P(r)$ denotes the radial dose function and $\phi_{an}(r)$ represents the 1D anisotropy function. For convenience, the report of the TG-43 suggests the use of the unit symbol U which represents $\mu$Gy m\textsuperscript{2} h\textsuperscript{-1}. To be consistent with the SPOT PRO\textsuperscript{TM} treatment planning system, the dosimetry calculations are done with the $r$-independent anisotropy constant $\overline{\phi_{an}}$ instead of $\phi_{an}(r)$, even if this approximation is no longer recommended since the update of the TG-43 report [13]. The characteristics of the
selectSeed\textsuperscript{TM}, detailed in table 2–3, were taken from a Monte Carlo study [14] and a thermoluminescence-based characterization of the seed [15]. This formalism assumes water-equivalent tissue, therefore it neglects the effect of tissue heterogeneities. However, Monte Carlo simulations have shown that taking into account the effect of tissue heterogeneities can result in differences in D\textsubscript{90} close to 5\% compared to water approximation [16].

Table 2–3: Physical characteristics of the selectSeed\textsuperscript{TM}.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>$A$</td>
<td>variable</td>
<td>mCi</td>
</tr>
<tr>
<td>Air-kerma strength conversion factor</td>
<td>$S_K/A$</td>
<td>1.27</td>
<td>U · mCi\textsuperscript{-1}</td>
</tr>
<tr>
<td>Air-kerma strength</td>
<td>$S_K$</td>
<td>variable</td>
<td>U</td>
</tr>
<tr>
<td>Dose rate constant</td>
<td>$\Lambda$</td>
<td>0.954</td>
<td>cGy · h\textsuperscript{-1} · U\textsuperscript{-1}</td>
</tr>
<tr>
<td>Anisotropy constant</td>
<td>$\phi_{an}$</td>
<td>0.936</td>
<td>-</td>
</tr>
</tbody>
</table>

As in any other radioactive decay process, the dose rate decreases in an exponential fashion:

$$\dot{D}(t) = \dot{D}_0 \times \exp \left[ \frac{-\ln(2) \cdot t}{\tau_{1/2}} \right] \quad (2.2)$$

where $\tau_{1/2}$ is the half life of the source, $\dot{D}(t)$ is the dose rate at a time $t$ and $\dot{D}_0$ is the initial dose rate. For a distribution with several seeds, the TG-43 formalism assumes a linear superposition of the dose distribution generated by each seeds. Thus, this dose calculation procedure neglects the interseed attenuation which can result in a drop in the D\textsubscript{90} parameter of 2\% to 6\% when taken into account [16]. Superposing the dose distribution for $N$ seeds and integrating equation 2.2 over an infinite time
allows to evaluate the cumulative dose $D_{\text{cum}}$ for permanent implants:

$$D_{\text{cum}} = \sum_{i=1}^{N} 1.44 \cdot \tau_{1/2} \cdot \dot{D}_0(r_i) \quad (2.3)$$

where $r_i$ denotes the distance between the source $i$ and the point-of-interest.

### 2.3 Postimplant dosimetry

Unfortunately, no matter how skilled are the physician and the other members of the clinical team, the real positions where the seeds are deposited are inevitably different from the planned positions [17, 7, 18]. The most important factors - human, mechanical and biological - explaining this discrepancy are listed below.

- Operator precision in the manual placement of needles.
- Prostate edema and bleeding caused by the stress of needle implantation.
- Gland motion (translation and rotation) due to needle implantation.
- Seeds migration inside or even outside of the prostate.
- Seeds displacement caused by the suction effect of needle retraction.

The combined effects of these different factors have a major impact on the dosimetry [19]. With a low energy isotope such as I-125, the dose distribution is highly dependent on the precise location of the seeds in relation to the target. The difference between the planned implant and the real seed distribution obtained raises the need for a postimplant dosimetric verification. The American Brachytherapy Society (ABS) recommends a CT-based dosimetry at a consistent postoperative interval [8]. The optimal time interval between the implantation and the postimplant dosimetry is controversial, but recent studies suggest that four weeks, the interval applied at our institution, may be the best time interval [20, 21].
The conditions to achieve a satisfying dosimetric coverage of the prostate and a limited dose given to the organs-at-risk are listed in table 2–4. On the other hand, the use of CT to obtain precise dosimetric information is questionable because of the difficulty to delineate properly the prostate [22]. It is recommended by the ABS to report the value of $D_{80}$, $D_{90}$, $D_{100}$, $V_{80}$, $V_{90}$, $V_{100}$, $V_{150}$ and $V_{200}$ to assess the quality of the implant [8]. However, the correlation between dosimetric parameters and PSA-based clinical outcomes has only been demonstrated for $D_{90}$ [9].

Table 2–4: Specific aims of the day-30 CT-based dosimetry.

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Urethra</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{100} &gt; 90%$</td>
<td>$V_{150} = 0$</td>
<td>$V_{100} &lt; 2\text{ cc}$</td>
</tr>
<tr>
<td>$V_{150} &gt; 58%$</td>
<td>$D_{90} &gt; 140\text{ Gy}$</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Intraoperative dosimetry

Following the implantation of the prostate, the more accurate dosimetric information available is the treatment plan corrected for needle deviation which are interactively adjusted during the implantation. A technique that could provide the postimplant intraoperative dosimetry information would be of great use to identify possible underdosage in the target. With increasing evidence of treatment effectiveness being correlated to postimplant dosimetry [23, 24], it is clearly desirable to assess intraoperatively the quality of the implant and to correct the sub-optimal
results, if needed. Furthermore, a new brachytherapy team would benefit from direct intraoperative dosimetric feedback to bypass the learning curve associated with the procedure [25]. In addition, the intraoperative dosimetry information would facilitate future correlation between dosimetric parameters and clinical outcome.

Such a postimplant dose evaluation requires to know precisely the seed positions and the related target contour. An ideal intraoperative dose assessment method should be done with the imaging devices commonly available in a LDR brachytherapy OR to limit extra time and cost to the procedure. CT scan is relatively good to image and localize the seeds and magnetic resonance imaging (MRI) is the gold standard to delineate the prostate. However these imaging modalities have limited availability and would require the patient to be moved from the OR to the imaging room and then possibly back to the OR. In addition, both CT and MRI have some issues related to seed detection. CT has problems to detect small seeds because of the large slice thickness, which can result in localization errors. In MRI, seeds are imaged as low signal regions that can be difficult to distinguish from other low intensity structures such as vessels or calcifications [26, 27]. Nonetheless, a low cost CT available in the brachytherapy room could be used for seed detection purpose.

2.4.1 3D seed position reconstruction

Intuitively, the TRUS probe, used to guide the procedure, would be an obvious resource to identify the seed positions. However, the poor quality of seed’s contrast in the image is very limiting and only a subset of the implanted seeds can be correctly manually identified [28, 29]. Furthermore, spacers or calcifications can be misinterpreted as radioactive sources. Nonetheless, a recent study in automatic seed
detection from 3D US images has achieved very good seed detection in phantom, but many problems related to clinical application need to be solved [30]. Advances in detection algorithm and TRUS technology may lead to a reliable TRUS-based seed detection system in the future. On the other hand, plane radiography, commonly available in the treatment room, provides very good seed visibility. Plane radiography can take the form of radiographic film, fluoroscopy or digital radiograph. Several methods have been developed to locate the 3D seed positions from two or more X-ray projections acquired isocentrically from different orientation. Most of them rely on a two-step process: (1) localizing the seed positions on each radiography and (2) matching each seed from one projection to the others. When the seeds are localized and matched, reconstructing the 3D positions is trivial.

The localization of the seeds on the radiograph, either manually or automatically, can be a difficult task due to the presence of overlapping seeds [31]. Automatic seed identification techniques can handle seed localization in small clusters of 2 or 3 overlapping seeds [32], but fail to correctly distinguish seeds in large clusters. Figure 2–4 shows a standard seed distribution where 57% of the 63 implanted seeds are located in clusters having two or more seeds. In some patient implant projections, there can be over 10 seeds overlapping in a single cluster.

The early attempts toward seed reconstruction proposed the use of two films [33], but this technique raised the problem of matching ambiguity. In fact, when two seeds and the two X-ray source positions are located in the same plane, there are two sets of possibly valid reconstructed 3D position (figure 2–5). The use of a third or a
fourth projection strongly reduces the risk of false positive detections, but the drawback is the mathematical complexity of the matching process. Matching images on three or more radiographs is an NP-hard (Nondeterministic Polynomial-time hard) problem. It is not practically possible to compute all the different possible combinations with 3 films because $N$ implanted seeds generate $(N!)^2$ possible matches. To give an order of magnitude, an implant with 60 seeds generates the colossal figure of $10^{164}$ possible solutions. Several methods have been developed to solve this problem [34, 35, 36, 37, 38], but they are limited by the requirement that all seeds must be accurately identified in each of the 2D projection data. Although certain methods can handle incomplete seed identification on the projections [39, 38, 31, 40, 41, 42], some seeds can still be missed if they are not detected on a minimum of two projections.

To get around the problem related to seed identification and matching, we developed in this study a tomosynthesis-based method that requires a higher number of
Figure 2–5: Ambiguity in film reconstruction. When backprojected, seeds \([A_1,A_2]\) and \([B_1,B_2]\) can either be reconstructed in their real position (black disk) or in a false position (white triangle).

Images than the three-film technique, but that does not require exact seed segmentation. Digital tomosynthesis (DTS) refers to a limited angle 3D image reconstruction using a small number of projection of an object using conventional X-ray systems. Some reconstruction algorithm based on DTS has been applied to seed detection [43, 44], but results were based either on simulations or phantom study. Consequently, these methods did not take into account issues related to clinical implants such as seeds clustering in the prostate or internal motion of the prostate. Our DTS method can reconstruct the 3D seed-only volume of a patient implant, i.e. a volume including solely the seeds, from a limited set of projections. Hence, the seed positions can be extracted from that reconstructed volume. DTS seed reconstruction offers several advantages over the three-film approach.
• DTS reconstruction does not require exact segmentation and localization of the seeds on the projections, which eliminates the need for manual correction on the projections,
• the use of several projections eliminate matching ambiguities,
• the computational complexity is greatly reduced and is independent of the number of implanted seeds, thus the reconstruction can be done very quickly.

2.4.2 Prostate contour co-registration

The lack of anatomical information is clearly a drawback with plane radiography. Thus, the prostate contour needs to be acquired with a different imaging modality than the reconstruction of the seed positions. The TRUS imaging is an appropriate modality to delineate accurately the prostate boundary, but it raises the need for a co-registration method with the seed positions. Several paths has been studied to answer this problem. The use of transperineal needle tips [45] or X-ray opaque markers attached to the TRUS probe [46] has been investigated to perform fusion between fluoroscopy and TRUS. However, these techniques are not applicable to our clinical set-up, because the patient cannot be moved under the X-ray field of view during the implantation. Indeed, the TRUS probe, the needle template and the seed delivery system are mounted on a fixed stalk, alongside of the treatment table. Thus, the TRUS probe must be taken off to move the patient. Then fiducial points detectable by both imaging modalities are required as a fixed standard of reference. The use of implanted gold markers inside the prostate has been clinically tested at our institution, but the fiducial markers could not be reliably distinguished from the radioactive sources on the ultrasound images. The implanted seeds can also be used
as markers to accomplish the fusion [47, 48, 49]. However, as mentioned previously, only a subset of the implanted seeds can be correctly identify on the TRUS images and the seed identification process is a tedious and error-prone task.

2.4.3 Dose coverage enhancement with intraoperative dosimetry

A few brachytherapy clinical teams have recently tested the capabilities of intraoperative dose assessment to improve the dosimetric coverage of the prostate. There can be two ways of using the intraoperative dosimetric information in order to improve the dosimetry: (1) adding remedial sources at the end of the procedure [50, 51, 52, 53, 54] or (2) readjusting dynamically the treatment plan during the procedure [55]. Of the two approaches, the former has raised more interest because of its greater simplicity. All of those studies, using various seed reconstruction and fusion techniques, have clearly demonstrated that prostate brachytherapy could be improved with the use of intraoperative dosimetry. The main drawback of these techniques is extra time and cost to the procedure.
Chapter 3
Image Acquisition and Processing

This chapter presents the different steps from image acquisition to image processing to format the plane radiographs into the proper format for the reconstruction of the 3D seed positions. These main steps are presented in the flowchart of figure 3–1. The first section of this chapter describes the acquisition process of the 7 images necessary to the tomosynthesis-based reconstruction. The following sections focus on the image processing step to remove the background and segment the seeds to generate seed-only images. Then, an additional filtration is applied to the seed-only images to improve the quality of the 3D seed reconstruction. All of the digital image treatment presented in this chapter were coded in MATLAB® (MathWorks Inc., Natick, MA) using functions included in the image processing toolbox.

3.1 Image acquisition

3.1.1 Description of the Simulix imager

The LDR brachytherapy treatment room at the Hôpital Notre-Dame is equipped with an isocentric imager, the Simulix Evolution™ (Nucletron, Veenendaal, the Netherlands) (figure 3–2). This latest generation simulator incorporates flat panel

![Flowchart of the seed extraction procedure.](image)

Figure 3–1: Flowchart of the seed extraction procedure.
detector and the option of cone beam CT (CBCT). Its 41×41cm amorphous silicon detector with a 1024×1024 pixel matrix provides a resolution of 0.4mm/pixel. This relatively high spatial resolution combined with good seed contrast make it a very good device to image brachytherapy seeds. A typical example of an anterior-posterior (AP) view of a patient implant acquired with the Simulix is given in figure 3–3.

Using a digital detector provides several advantages over film radiographs: it saves acquisition time, reduces positioning uncertainty and provides numerical data
ready to be analyzed. A fluoroscopy unit could be used as well for seed imaging purpose, but the distortion generated by the image intensifier needs to be corrected. In addition, mechanical uncertainty related to source and film positioning is greater and patient dose is larger with a conventional fluoroscopy unit compared to flat panel technology.

3.1.2 Acquisition geometry

The coordinate system presented in figure 3–4 will be used throughout this seed reconstruction study. The source-to-axis distance (SAD) is fixed at 100 cm, while the source-to-detector distance (SDD) is variable. Right after the implantation, the patient is lying in the \( xy \) plane with his head pointing toward the \( y \)-axis (see figure 3–4). The patient is imaged in this set-up, while he is still under anaesthesia, right after the prostate implantation. The tomosynthesis-based reconstruction algorithm, presented in chapter 4, requires 7 images acquired at various gantry angles: -30°, -20°, -10°, 0°, 10°, 20° and 30°. To avoid localization imprecision caused by small
parallaxes in 3D seed reconstruction, the gantry angles ($\theta$) between each projection are chosen as large as possible [56]. On the other hand, the choice of gantry angle is limited by the body anatomy because lateral images suffer from poor seed contrast due to bony structures and patient thickness. The best quality images are obtained with gantry angle between $-35^o$ and $35^o$ [32]. The choice and sequence of the following operations follow that from a paper by Tubic et al [32].

3.2 Background removal

The input to our tomosynthesis-based reconstruction algorithm is 7 seed-only images from different projection angles, thus the first step toward seed position reconstruction is to process each projection to generate seed-only images. The technique to generate seed-only images is fully automatic, except for the selection of the region of interest in the image which is user dependent (figure 3–5).
Figure 3–6: Influence of the log transformation followed by the normalization. (a) Original image. (b) Normalized image.

**Normalization.** A simple thresholding of the cropped image is not sufficient to properly segment the seeds because some bone regions can have either smaller or larger intensity than the seeds. Thus, some preliminary steps are implemented to attenuate the background and therefore to increase seed contrast. The gray-level intensity of the seeds depends on the patient body structure and thickness as shown by equation 3.1:

\[
\frac{I}{I_0} = \exp \left[ - \int_{L_{\text{seed}}} \mu_{\text{seed}}(x, y, z) dl - \int_{L_{\text{tissue}}} \mu_{\text{tissue}}(x, y, z) dl \right]
\]  

(3.1)

where \(I/I_0\) is the attenuation of the incident intensity, \(\mu\) is the attenuation coefficient and \(L_{\text{seed}}\) and \(L_{\text{patient}}\) are respectively the X-ray path length through the seed and the patient. To limit the influence of the structure thicknesses on the resulting signal intensity, the value of each pixel of the image is converted with equation 3.2 so that the resulting intensity represents a simple linear sum of attenuation coefficients of
the seeds and the body:

\[ b_{i,j} = \log(a_{i,j} + 1) \]  

(3.2)

where \( a_{i,j} \) is the original value of the pixel located at the coordinate \((i, j)\) and \( b_{i,j} \) is the modified value. This transform is comparable to CT scan reconstruction, where the intensity along a ray must be converted to a sum of attenuation coefficients of the voxels along its path. The same principle applies to seed detection. Following this transformation, the value of each pixel is normalized over the gray scale going from 0 to 255 (equation 3.3):

\[ b_{i,j} = \frac{b_{i,j} - b_{\text{min}}}{b_{\text{max}} - b_{\text{min}}} \times 255 \]  

(3.3)

where \( b_{\text{min}} \) is the minimal and \( b_{\text{max}} \) the maximal pixel value of the image. This enhances the image contrast by spreading the pixel values over the whole gray scale range. The effect of equation 3.2 and 3.3 is presented in figure 3–6 where one can already notice a clear improvement of the seed contrast with the background.

**Morphological mathematics.** Before proceeding to the automatic thresholding of the normalized image presented in figure 3–6, the background of the radiograph needs to be as uniform as possible. However, the non-uniformity of patient thickness and the presence of bony structures lead to a non-uniform background, which is problematic for appropriate seed extraction. To solve this problem, morphological mathematics [57, 58] is used to attenuate the background on the image. Mathematical morphology is a theory and technique providing an approach for the analysis and treatment of digital images. There are two basic operators in morphological image processing from which all the other operators are based: erosion
Figure 3–7: Influence of the background removal on the image (left row) and on the pixel value corresponding to the red line (right row). (a,b) Normalized image. (c,d) Background image. (e,f) Background subtracted from the normalized image.
(equation 3.4) and dilatation (equation 3.5). These two operations require a structuring element \( k \) which is applied over the image \( im \) to be processed.

\[
\text{Erosion}(im(x, y), k) = \min \{ im(x + i, y + j) - k(i, j) \}, \quad (i, j) \in W
\]

\[
\text{Dilatation}(im(x, y), k) = \min \{ im(x - i, y - j) + k(i, j) \}, \quad (i, j) \in W
\]

Where \( W \) is the support of the structuring element. As we can see in figure 3–7(a) and 3–7(b), the normalized image is composed of a certain background and of “holes” representing the seeds. To isolate the background, we need to remove these holes. Applying successively a dilatation followed by an erosion to the image can achieve this when the structuring element is larger than the holes. The shape of the chosen structuring element \( k \) is a disk with a radius of 6 pixels. The result of this operation, called morphological closing, when applied to the normalized image is an approximation of the background (figure 3–7(c) and 3–7(d)). Subtracting the background from the normalized image provides a clear improvement of the seed contrast. In the morphological mathematics field, this operation is called bottom-hat filtering. Black and white scales are inverted on this filtered image (figure 3–7(e) and 3–7(f)).

### 3.3 Seed segmentation

**Wiener filtering.** Before proceeding to automatic thresholding, a Wiener-filtering step is applied to the image. The goal of the 2D Wiener filter is to filter out noise corrupting the signal. This filter is based on a statistical approach using the information given in the neighborhood of each pixel [59]. Limiting this neighborhood to a region of 5x5 pixels, the background noise is smoothened while the seed signal
is not significantly affected (figure 3–8(a) and 3–8(b)). This reduces the chance that bony structures are get segmented as seeds.

**Automatic thresholding with Otsu method.** The intensity of the seed and of the background can vary significantly from one patient to another and from different projection angles. Thus the intensity level of the threshold cannot be a fixed value to separate the seeds from other objects. Moreover, a manual selection of this threshold is undesirable, because the seed reconstruction process needs to be as automated as possible. This problem can be solved using the Otsu algorithm [60] which uses the information in the histogram to separate the pixels into two different classes: background and foreground (seeds). The optimal threshold will separate the pixels into two classes so that the combined within-class variance is minimized. This is equivalent to minimizing equation 3.6:

\[
\sigma_w^2(t) = q_1(t)\sigma_1^2(t) + q_2(t)\sigma_2^2(t) \tag{3.6}
\]
where $\sigma_w$ is the combined variance, $\sigma_i$ is the inner-class variance, $q_i$ is the probability for a pixel to be in class $i$ and $t$ is the intensity threshold value. This algorithm assumes a uniform illumination, which raises the importance of removing the background. Figure 3–9 presents the result of the seed binarization where the selected threshold clearly segments the seeds and rejects the background.

A simple connected-component analysis is performed on the binary image to remove very small structures with an area smaller than 10 pixels. These small regions are likely to be segmentation fault because the average area for one seed is 37 pixels.

### 3.4 Specific filtration for tomosynthesis reconstruction

An additional filtration step needs to be performed on the binary seed-only images before feeding it into the tomosynthesis reconstruction algorithm. The goal here is to give more importance to the pixels that are located at the center of the segmented areas relatively to the pixels that are on the periphery. To accomplish this, we give an additional value of $1/8$ for each white pixel directly surrounding the
Figure 3–10: Binary image filtration providing an image with the center of the segmented areas given more intensity than the periphery. (a) Binary image. (b) Filtered image.

A pixel of interest (equation 3.7). Thus, a pixel located in the center of a cluster can have a maximal intensity value of 1.5. The \(1/8\) factor was optimized to provide the most accurate reconstruction of the tomosynthesis-based volume with the procedure developed in chapter 4.

\[
p_{i,j} = p_{i,j} + \frac{1}{8} (p_{i+1,j} + p_{i-1,j} + p_{i,j+1} + p_{i,j-1})
\]

(3.7)

Where \(p_{ij}\) is the intensity of the pixel located at \((i,j)\). The result of this filtration for a specific seed cluster in a patient implant is presented in figure 3–10.

### 3.5 Additional time to the procedure

The image acquisition and processing is the first step toward seed position reconstruction and it needs to be done rapidly to limit the additional time to the procedure. The image acquisition is not in itself an extra step to the standard procedure, because the clinical team always takes 3 radiographs right after the implantation, an AP, -30° and 30° view. Thus, only 4 additional radiographs need to be taken to complete the image set. These extra radiographs are taken in approximately 5
minutes. The computation time to open the dicom files, remove the background, segment the seed and filter the binary images is almost negligible with an average of 0.75 second/image. The manual selection of the region-of-interest (ROI) is the most time consuming task related to image processing. The whole image treatment, including the manual selection of the ROI and the automatic image processing for the 7 images, takes an average of 55 seconds. In summary, an extra time of 6 minutes is needed to acquire the radiographs and to process them into the proper format for the tomosynthesis-based reconstruction algorithm. However, the availability of an automated scan motion for the image acquisition could drastically bring down the image acquisition time to a few seconds. This would reduce the total extra time to approximately one minute.
Chapter 4
Tomosynthesis-based Seed Reconstruction

Tomosynthesis can be defined as the creation of a 2D or 3D image of an object by digital processing of multiple X-ray projections acquired over a limited angle of view. In our case, the goal is to reconstruct a volume including the implanted seeds and to localize the seeds centroid inside this reconstructed volume. The first section of this chapter describes thoroughly the tomosynthesis-based reconstruction algorithm and the determination of the seed positions inside this volume. To test the validity of this seed localization method, section 4.2 presents the results of the phantom study and section 4.3 presents the results of the clinical study.

The geometry of the tomosynthesis projections acquisition is presented in figure 4–1 where \( \Theta \) represents the tomosynthesis angle defined as the angular range between the two extreme gantry positions. The center of the global coordinate system \((x, y, z)\) is the isocenter of the simulator and the center of the projection coordinates \((u, v)\) is the center of the detector.

4.1 Tomosynthesis-based algorithm

As was presented in chapter 3, preliminary image processing is performed to format the raw projection images (figure 3–5) into seed-only images (figure 3–9) and then to filtered seed-only images (figure 3–10). The main input to our tomosynthesis-based reconstruction algorithm is seven filtered seed-only images acquired at \( \theta = -30^\circ, -20^\circ, -10^\circ, 0^\circ, 10^\circ, 20^\circ \) and \( 30^\circ \). In tomosynthesis, the larger is the number of images,
Figure 4–1: Tomosynthesis geometry of acquisition. \( x, y \) and \( z \) denote the global coordinates while \( u \) and \( v \) denote the projection coordinates on the flat panel detector.

the better is the reconstruction quality. However, seven images is enough to provide reasonable reconstruction quality without adding too much time to the procedure and unnecessary dose to the patient. The tomosynthesis-based reconstruction algorithm can be summarized in a two-step process: (1) reconstruction of a seed-only volume from the 7 filtered images and (2) localization of the seed positions from a 3D connected component analysis.

4.1.1 Seed-only volume reconstruction

From the seven filtered seed-only projections, the objective is to reconstruct a seed-only volume, i.e. a volume including exclusively brachytherapy seeds. This is done with the 3 following steps, inspired by Tutar et al. work [43].

1. Determination of the prostate center \((X_c,Y_c,Z_c)\)
2. Reconstruction of the volume by backprojection
3. Binarization of the reconstructed volume

**Prostate center.** The first step is to localize in space the approximate prostate center from the X-ray projections. To achieve this, the center of mass of the binary seed-only image is computed with equation 4.1 for the projections taken at -30°, 0° and 30°:

\[
(u_c, v_c) = \frac{1}{N} \sum_{i \in W} (u_i, v_i)
\]

where \((u_c, v_c)\) is the projected center of the cloud of seed, \(W\) is the set including all the white pixel regions, \((u_i, v_i)\) is the position of the \(i^{th}\) white pixel and \(N\) is the number of white pixels. Then the equations of the lines joining these 3 centers of mass with their corresponding X-ray sources are computed. Finally, the approximate prostate center \((X_c, Y_c, Z_c)\) is provided by the point minimizing the distance between those three lines. The volume to be reconstructed is centered at \((X_c, Y_c, Z_c)\) and is given the dimension of the prostate, coming from the TRUS contours, \(\Delta X_{\text{prostate}}\), \(\Delta Y_{\text{prostate}}\) and \(\Delta Z_{\text{prostate}}\) plus an extra margin of 1 cm to include seeds that might have been deposited outside of the prostate boundaries.

**Backprojection.** The reconstructed volume needs to have a very good spatial resolution because of the small size of the objects to detect. A single seed has a radius of 0.4 mm and a length of 4.5 mm. To correctly reconstruct the geometry of the seeds, the volume is reconstructed with a resolution of 0.25×0.25×0.25 mm\(^3\). Since the resolution of the flat panel detector is 0.4 mm and the magnification factor of the seeds is approximately 3/2 (depending of the detector position), a voxel resolution of 0.25 mm is the minimum value to conserve the detector information. For each voxel located in \((x,y,z)\), the corresponding coordinates \((u,v)\) can be found by projecting
the 3D point on the 2D detector, from the X-ray source point of view. The projected coordinates \((u,v)\) are computed on the seven projections using equations 4.2 and 4.3 [61, 62, 43]:

\[
\begin{align*}
  u &= SSD \times \frac{-z \times \sin(\theta) + x \times \cos(\theta)}{SAD - z \times \cos(\theta) - x \times \sin(\theta)} \\
  v &= SSD \times \frac{y}{SAD - z \times \cos(\theta) - x \times \sin(\theta)}
\end{align*}
\] (4.2) (4.3)

where \(\theta\) is the gantry angle, SAD the source to axis distance and SSD the source to detector distance. Then, for a voxel located in \((x_i, y_i, z_i)\) with its corresponding coordinates \((u_{ij}, v_{ij})\) in the projection \(j\), the voxel intensity is calculated with equation 4.4:

\[
I_{3D}(x_i, y_i, z_i) = \sum_{j=1}^{7} I_{2D}(u_{ij}, v_{ij})
\] (4.4)

where \(I_{3D}(x_i, y_i, z_i)\) is the voxel intensity at the point \(i\) and \(I_{2D}(u_{ij}, v_{ij})\) is the corresponding pixel intensity on the filtered seed-only projection \(j\). Since \(I_{2D}(u_{ij}, v_{ij})\) value varies from 0 to 1.5, the intensity scale of the reconstructed volume goes from 0 to 10.5. The intensity of each voxel included in the reconstructed volume is computed. Figure 4-2 represents one axial slice of the reconstructed volume for a patient implant. In this figure, seeds can be located in the regions of high intensity where the backprojected seed images converge.

**Binarization.** From figure 4-2, we can see that only the presence of seeds generates regions of high intensity. Then we can simply extract these seed regions with the application of a threshold to generate a seed-only binary volume. From experimentation, an intensity value of 7 has shown to be an appropriate threshold to correctly segment the seed, without including reconstruction artifacts. The choice
of a threshold value of 7 was carefully optimized to minimize the possibility of false-positive detection and to maximize the number of seeds detected. An example of a seed-only volume is presented in figure 4–3 where we can clearly observe that only the implant is visible after the thresholding operation. From the tomosynthesis reconstruction properties, the resolution is much better in the $x - y$ plane than in the vertical dimension ($z$) because of the limited image acquisition angle [56]. When some implanted seeds into the prostate are very close in the $x - y$ plane or relatively close in the $z$ direction, they aggregate in large clusters of connected voxels into the seed-only volume. This clustering effect is very likely when using loose seeds. From the analysis of 10 patient implants, we evaluated that approximately 40% of the seeds were included in such an aggregate composed of two (28%), three (10%) or four (2%) seeds.

4.1.2 3D connected component analysis

The aim of the 3D connected component analysis is to determine the position of each seed in the reconstructed seed only volume. The main challenge is to identify
the seed centroids in the clusters of connected voxels including more than one seed. To achieve this, a statistical classifier based on the cluster’s geometrical properties is generated to determine the number of seeds in each cluster. The number of implanted seeds is used as an upper limit to the total number of detected seeds, but not as an aim since the number of seeds in the prostate may be inferior to the number of implanted seeds. In fact, the main issue in seed fixicity in the prostate is seed migration to the lung through embolization [63, 64, 65]. The global 3D connected component procedure is summarized by the flowchart in figure 4–4.

**Cluster’s geometrical characteristics**

Clusters of connected voxels are defined with 26-connectivity, i.e. any two neighboring binarized voxels are considered as part of the same cluster. A first analysis is performed to discard all the clusters with a volume smaller than 40 voxels which are considered like reconstruction artifacts. This number of voxels corresponds to a volume of 0.625 mm$^3$ while the actual volume of a seed is approximately 2.25 mm$^3$. 

Figure 4–3: Seed-only reconstructed volume.
Figure 4–4: 3D Connected component analysis flowchart.
Then each remaining cluster is characterized based on its geometrical characteristics. An ellipsoid fitting is performed on each cluster [66] to extract the length of the major axis $a$, intermediate axis $b$ and minor axis $c$, and the orientation of the major axis. The comparison between the real and reconstructed seed dimensions is presented in table 4–1. The discrepancies between the real and reconstructed dimensions is mainly due to the poor resolution in the vertical ($z$) direction. Since the seeds are globally oriented toward the $y$-axis, one of their small axis $b$ tend to be stretched vertically.

<table>
<thead>
<tr>
<th>dimensions</th>
<th>$2\times a$ (mm)</th>
<th>$2\times b$ (mm)</th>
<th>$2\times c$ (mm)</th>
<th>volume (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>real</td>
<td>4.5</td>
<td>0.8</td>
<td>0.8</td>
<td>2.25</td>
</tr>
<tr>
<td>reconstructed</td>
<td>4 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>0.7 ± 0.1</td>
<td>2.1 ± 0.6</td>
</tr>
</tbody>
</table>

**Statistical classifier**

A statistical classifier based on the following identification function $ID$ (equation 4.5) is used to evaluate the number of seeds per cluster. Obviously, the larger the value of the $ID$ function is, the larger is the number of seeds in the cluster.

$$ID = \frac{a}{\langle a \rangle_{1\text{seed}}} + \frac{b}{\langle b \rangle_{1\text{seed}}} + \frac{c}{\langle c \rangle_{1\text{seed}}} + \frac{volume}{\langle volume \rangle_{1\text{seed}}}$$ (4.5)

Where $\langle a \rangle_{1\text{seed}}$, $\langle b \rangle_{1\text{seed}}$, $\langle c \rangle_{1\text{seed}}$, and $\langle volume \rangle_{1\text{seed}}$ are the average geometrical properties for a single seed. To correlate the $ID$ values with the number of seeds per cluster, 177 clusters in 12 patients were analyzed and are presented in the histogram.
on figure 4–5. From this histogram, ranges of ID value were established to classify the number of seeds in each cluster (table 4–2). It would be unlikely to find more than 4 seeds in such a cluster, so this is the chosen upper limit. From figure 4–5, we can see that the cluster assignment is not flawless because some ID values overlap from one class to the next. However, the classifier provides the proper number of seeds in 97% of the cases. To improve the classifier efficiency, the algorithm modifies the classification if the number of detected seeds exceeds the number of implanted seeds. This re-classification relies on the $ID_{prob}$ value (equation 4.6) that evaluates which cluster is the more likely to overestimate the real number of seeds. As long as the total number of detected seeds exceeds the number of implanted seeds, the cluster with the smallest $ID_{prob}$ value is reassigned with a number of seeds reduced by one.

\[
ID_{prob} = \frac{ID - \langle ID \rangle_{Nseed}}{\langle ID \rangle_{Nseed}}
\]  

(4.6)

Table 4–2: ID average values and ranges as a function of the number of seeds

<table>
<thead>
<tr>
<th>Number of seeds</th>
<th>$\langle ID \rangle_{Nseed}$</th>
<th>ID range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.9</td>
<td>[0-5.2]</td>
</tr>
<tr>
<td>2</td>
<td>7.5</td>
<td>[5.2-10]</td>
</tr>
<tr>
<td>3</td>
<td>13.5</td>
<td>[10-20]</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>$\geq 20$</td>
</tr>
</tbody>
</table>

At this point, the number of seeds in each clusters is known so the next step is to localize the centroid of each seed. This is done differently depending on the number of seeds in the analyzed cluster.
Figure 4–5: Clusters classification as a function of their $ID$ function value for 177 clusters analyzed.
• **Clusters including 1 seed**

The seed centroid is simply the center of mass of the cluster of connected voxels:

\[
(X, Y, Z) = \frac{1}{N} \sum_{i \in W} (X_i, Y_i, Z_i)
\]  

(4.7)

where \(W\) is the set of all voxels in the clusters.

• **Clusters including 2 seeds**

In this case, the 2 seeds are disposed along the major axis, one located at \(-2 \times a/3\) and the other at \(2 \times a/3\) from the cluster centroid.

• **Clusters including 3 or 4 seeds**

If a cluster is classified with a number of seeds \(N\) larger than 2, the grid of connected voxels is resampled on a \(3 \times 3 \times 3\) grid. Then the seed centroids are defined as the center of the \(N\) resampled voxels with the highest intensity.

When a cluster is assigned with more than one seed, the seed positioning is done fairly approximately. This approximative seed placement has a significative influence on the distribution of hot spots, but has almost no impact on the presence of cold spots. Since the final aim of intraoperative dosimetry is to localize cold spots, those approximations are reasonable as confirmed by the following phantom validation and patient study.

4.1.3 **Computation time**

To implement an intraoperative seed detection method in the clinic, the computation time needs to be as short as possible. The tomosynthesis-based algorithm has the advantage over the three-film technique that it is less computationally-intensive.
In the three-film method, the computation time increases very steeply with the number of implanted seeds while the tomosynthesis-based computation time is simply proportional to the size of the reconstructed volume. However, the initial version of the algorithm, entirely coded in MATLAB, was relatively slow taking approximately 4 minutes on a 1.8 GHz pentium Dual PC to reconstruct and display the seed positions from the pre-processed images. MATLAB scripts are notoriously slow when large loops are involved. Two sections of the MATLAB code using such large loops, the backprojection and the analysis of the reconstructed volume, were re-coded in C++, a faster execution code. This improvement reduced the computation time by almost an order of magnitude to an average of 36.5 seconds when run on the same computer. More than 99% of the computation time is spent to backproject the information of the 7 images into the reconstructed volume. The execution speed could be further improved using graphics processing units (GPUs). GPUs are suited for this application, because tomographic reconstruction is an inherently parallel algorithm. The use of these massively parallel devices can lead to an increase of the speed by a factor up to 30 which would result, in our case, in a total computation time of the algorithm in less than a few seconds [67].

4.2 Results: Phantom validation

4.2.1 Phantom description

We used a tissue-equivalent prostate phantom (Model 053, Computerized Imaging Reference Systems, Norfolk, VA) to validate our tomosynthesis-based seed detection algorithm. The phantom, presented in figure 4–6, includes several organs: prostate, seminal vesicles, rectal wall and urethra. The phantom is embedded in a
11.5 cm×7.0 cm×9.5 cm clear acrylic container and the different organs are made of water-equivalent gel, Blue Zerdine® and Zerdine®. The phantom was implanted with 45 non-radioactive seeds (4.5 mm long × 0.4 mm radius, Nucletron dummy seeds) under TRUS guidance for needle placement through a brachytherapy template. The seed positions were generated with the SPOT PRO™ treatment planning system to produce a typical clinical treatment plan. The difference with a patient implantation procedure was the manual placement of the seeds inside the needles, which led to additional seed positioning uncertainty compared to the initial plan.

4.2.2 Positioning uncertainty

To evaluate the positioning uncertainty, the implanted phantom was imaged under a CT scan with very small slices of 0.4 mm to obtain the best achievable resolution. The seed centroids were extracted from the CT volume with the SPOT PRO™ seed localization utility. To co-register the CT-based seed positions and the tomosynthesis-based seed positions, five fiducial markers, visible on CT and on the simulator images, were placed on the surface of the phantom. The 3D position of
the markers in the simulator frame of reference were reconstructed from the -30° and +30° projections while the position in the CT reference were manually identified in the 3D volume. The fusion was simply done by finding the solid transformation providing the best fit between the two sets of points. Figure 4–7(a) presents very good agreement between the tomosynthesis-based seed position and the CT “gold standard” reference. From a one to one correspondence between the two sets of positions, we evaluated that the average localization error was 0.4±0.4 mm and that 96% of the reconstructed seed positions are within 1 mm from the CT standard position (figure 4–7(b)). However, since results were not obtained on a precisely machined phantom with known seed positions, the intrinsic precision of the reconstruction algorithm is not known. The localization error in this study refers to the difference in CT-based and tomosynthesis-based seed positions.
To evaluate the dosimetric impact of the positioning uncertainty, the dosimetry calculation generated with CT seed positions is compared with the dosimetry generated with tomosynthesis-based seed positions. From the results of this comparison, presented in Table 4–3, we can conclude that there is no significant differences in the main dosimetric parameters.

<table>
<thead>
<tr>
<th></th>
<th>$D_{80}$ (Gy)</th>
<th>$D_{90}$ (Gy)</th>
<th>$D_{100}$ (Gy)</th>
<th>$V_{80}$ (%)</th>
<th>$V_{90}$ (%)</th>
<th>$V_{100}$ (%)</th>
<th>$V_{150}$ (%)</th>
<th>$V_{200}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-based</td>
<td>151.5</td>
<td>118.9</td>
<td>61.6</td>
<td>91.1</td>
<td>82.6</td>
<td>48.8</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>Tomosynthesis-based</td>
<td>151.6</td>
<td>119.5</td>
<td>61.9</td>
<td>91.2</td>
<td>82.5</td>
<td>48.8</td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td>Difference (%)</td>
<td>0.1%</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

### 4.2.3 Seed orientation

The seed reconstruction algorithm provides the orientation of each cluster of connected voxels from the ellipsoid fitting. Therefore, the seed orientation can only be determined precisely when a cluster includes only one seed in it. The implanted prostate phantom was used to assess the error on the seed orientation reconstruction. First, the orientation has been manually measured from the CT scan data (uncertainty estimated at $5^\circ$) and then compared with the tomosynthesis-based reconstruction method. From this analysis, the seed orientation reconstruction error is $10^\circ \pm 8^\circ$. When a cluster of connected voxels includes more than one seed, then the global orientation of the cluster can be used as a gross approximation of the individual orientation of each seed. However, due to the small impact of seed orientation on
prostate dosimetry [68], all the dosimetric calculations of this study are performed with point source approximation, as recommended by the AAPM Task Group No. 64 (TG-64) [7]. In addition, the point source approximation is also used clinically by the treatment planning system, even if SPOT PRO™ does support 2D line source dose calculation. Nonetheless, the seed orientation can have a significant impact on the dose delivered to the OARs [68].

4.3 Results: Patient study

The phantom study is a first step toward the validation of our algorithm, however the real testing needs to be done on patient implants. The main pitfall of the phantom study is that it neglects the prostate internal motion, which is usually quite small but not always negligible. The quality of the automated reconstruction output was evaluated for 25 patients implanted at the Hôpital Notre-Dame. From these 25 patients, two were discarded from the study because the quality of the reconstruction was very poor. The first one woke up from anesthesia during the image acquisition
Figure 4–9: Comparison of (a) an AP view of a patient implant with (b) the projection of the reconstructed volume from the same view.

and the second one presented abnormal prostate motion during the imaging process. A quick and automated image acquisition would limit the risk of patient or organ motion during the imaging sequence.

An example of reconstructed seed positions projected on the simulator images is presented in figure 4–8. A simple visual inspection of the image shows that the 3D seed position markers are projected very close to the centroid of the seed images. Figure 4–9 illustrates that the reconstructed volume projected in the AP view (figure 4–9(b)) is very similar to the seeds visible in the corresponding radiograph (figure 4–9(a)). The most obvious discrepancies between the original and the reconstructed projection are generated in the regions of high seed density, where the original seed geometry becomes less distinct. From the same figure, it is clear that the seed orientation is accurately conserved, for most of the seeds, in the reconstruction process.
4.3.1 Reconstruction efficiency

From the analysis of the 23 valid patients, the seed reconstruction algorithm has shown to accurately retrieve 96.7% of the implanted seeds. Thus, 3.3% of the implanted seeds are undetected while 2.6% of the total number of seeds are falsely detected (false-positive). Most of the reconstruction flaws come from errors of the statistical classifier that can over or under estimates the number of seeds in the clusters. The seed reconstruction errors generally happen in regions of high seed density. Indeed, these high seed density regions are subject to shadowing artifacts, especially in the AP direction because of the limited tomosynthesis angle of acquisition. These artefacts can either result in distorted seed geometry or large clusters of connected seeds. Based on simulation study, it has been shown that 95% or more seeds need to be localized in order to obtain a $D_{90}$ value within 5% of the real value [69]. Results presented in section 4.3.2 confirm that the 96.7% seed detection rate combined with a 2.6% of false-positive can provide fairly accurate dosimetry.

4.3.2 Impact of reconstruction error on the dosimetry

To evaluate the effect of these errors on the prostate dosimetry, the reconstruction errors were manually corrected for 15 patients using the graphical user interface (GUI) tools presented in chapter 7. Figure 4–10(a) presents a case with several obvious errors and figure 4–10(b) presents the same case, but manually corrected. Then the dosimetry of the automatic and the corrected reconstruction were compared to assess the impact of these corrections. Results, summarized in table 4–4 in terms of relative mean difference and standard deviation, show little difference in the two main parameters $D_{90}$ and $V_{100}$. For the worst of the 15 patients analyzed (see figure
Figure 4–10: Manual correction of reconstruction flaws (encircled regions). (a) Automatic reconstruction. (b) Manual corrections.

4–10), the difference in $D_{90}$ and $V_{100}$ is respectively 3% and 1.4%. The dosimetric parameters that are the most influenced by the reconstruction flaws are the $V_{150}$ and $V_{200}$ which indicates the volume of the prostate receiving very high dose. This brings us to conclude that the reconstruction errors mostly influence the hot spots distribution while it has little impact on the presence of cold spots and on the medium dose distribution. The analysis of the isodoses for several patient implants present significant deviations between the automatic and the corrected dose distribution mostly for 200 Gy isodose lines and larger dose.

4.4 Conclusion

The phantom study demonstrates that the reconstruction accuracy of the seed position is sub-millimetric and the patient study presents a seed detection rate that provides dosimetric parameters very close to reality. Since most of the seed detection
errors come from the analysis of the 3D clusters including several seeds, this reconstruction technique would provide even better results with suture-mounted seeds (e.g. RAPID Strand™, Oncura, Arlington Heights, IL). Indeed, seed aggregation is less common with stranded seeds which would reduce the risk of errors coming from the statistical classifier or approximate seed placement in clusters of 3 or 4 seeds. However, the results presented in this chapter clearly show that our reconstruction method can provide satisfying dosimetry, even with loose seeds. In addition, the algorithm can determine the seed positions fairly quickly, in an average of 36 seconds, independently of the number of seeds. This reconstruction technique would probably be less effective in a center using very low activity seeds which would imply close to 120-125 seeds. Indeed, a higher seed density would imply more seed aggregation and more seed detection errors. Nevertheless, all the different seed detection technique are less efficient when a very large number of seeds are densely implanted.
Chapter 5
Prostate Contour Co-Registration

The fusion, or co-registration, between the reconstructed seed position and the prostate boundaries is an inevitable step to perform accurate organ dosimetry calculations. The transformation matrix allowing to convert one image set to the other characterize the fusion. The availability of both seed positions, acquired with plane radiography, and prostate contour, obtained with the TRUS probe, leads instinctively to the co-registration between these two imaging modalities. The dosimetry information is computed with the postimplant prostate contours, which are acquired at the very end of the implantation procedure.

One of the limitation on the accuracy of our dosimetry calculation comes from the deformation of the prostate due to the TRUS probe pressure. On one side, the seed positions are reconstructed after the probe has been taken off from the rectum and, on the other side, the prostate contours are obviously acquired with the probe in. As a first approximation, it seems reasonable to neglect the deformation due to the probe pressure since the prostate roughly behave as a rigid body [70]. Nevertheless, a visual inspection of the central slice of a TRUS and a CT prostate contour, as shown in figure 5–1, reveals a slight deformation of the posterior part of the prostate.
In this chapter, we describe a fusion technique that requires negligible extra time to the procedure and that is fully automated. The method, described in the following section, uses the planned seed position as a reference in the ultrasound frame of reference (plan-based fusion). To validate this procedure, the fusion results using this method were compared with another procedure based on seed identification in the ultrasound images (seed-based fusion) [47, 48, 49]. The methods and materials section describes in detail both of these co-registration technique. Differences between these two methods, for 17 patients, in terms of positioning uncertainty and dosimetric impact are presented in the results section to validate our method.

5.1 Methods and materials

5.1.1 Fusion method: Plan-based co-registration

The plan-based fusion uses the planned seed positions, corrected for needle placement, as a reference in the TRUS coordinate system which includes the prostate contour. These planned seed positions are used as the target points to match the

Figure 5–1: Comparison of the prostate central slice of a (a) CT contour and (b) TRUS contour for the same patient. The arrows represent the pressure of the TRUS probe resulting in a deformation of the posterior part of the prostate.
reconstructed seed positions. The rotation \((R)\) and the translation \((T)\) minimizing the distance between the two clouds of points, planned and reconstructed positions, are calculated with the iterative closest point (ICP) algorithm [71]. This very simple algorithm is commonly used in real-time application to quickly find the solid transformation between two sets of points. This algorithm always converges toward the nearest local minimum of a mean-square distance cost function. Thus to ensure that the local minimum is actually the global minimum, the input positions need to be a first approximation of the transformation. Essentially, the steps of the ICP algorithm are listed below:

1. Apply as a first approximation a translation to match the center of mass of the two clouds of points.
2. Associate points with the nearest neighbor criteria.
3. Exclude association of points with a distance larger than 3 mm.
4. Estimate \(R\) and \(T\) using a mean-square cost function.
5. Transform the points using estimated \(R\) and \(T\).
6. Iterate 2 to 5 until convergence.

Once the ICP algorithm is applied, the reconstructed seed positions are transferred into the TRUS coordinate system, which allows dosimetric calculation with the availability of the anatomical spatial information. This fusion algorithm is computed in a negligible time of 0.1 second. An example of the fusion between the two sets of points for a patient implant is presented in figure 5–2. The two sets of points are globally matching, but a one-to-one correspondence between the two sets is a difficult
Figure 5–2: Co-registration resulting from the fusion between the planned seed positions (o) with the reconstructed seed position(*).

task, especially in the regions of high seed density. The validity of this co-registration technique relies on two assumptions:

1. The difference between the planned seed positions and the real deposited positions is smaller than 3 mm for a significantly large number of seeds.

2. There is no global shift, in any direction, between the planned and the real deposited seed positions.

The first assumption is a criteria for our ICP algorithm to find a good match between the two sets of points. Because this fusion technique uses a relatively large number of points to retrieve the solid transformation, the individual one-by-one errors should globally cancel out, if they are small enough. Secondly, a systematic shift between the planned and the real seed positions would generate an equivalent shift between the reconstructed seed positions and the co-registered contours. These assumptions
Figure 5–3: Manual identification of the seeds on the TRUS images. (a) Slice of an original image with planned seed position (o). (b) Same slice with manually identified seed centroids (o).

are hard to assess clinically, so another co-registration method, described in the next section, is used to validate this fusion technique.

5.1.2 Validation method: Seed-based co-registration

The identification of deposited seed position from a TRUS image set is a time consuming, error prone and tedious task. For these reasons, a co-registration method relying on the localization of the seeds on the TRUS image (seed-based registration) is unsuitable for intraoperative purposes. Performing the fusion in the OR requires indeed a quick and very robust method. However, by carefully stepping through the 0.3 mm slices of the TRUS volume, it is possible to localize a subset of the implanted seed centroids. Therefore this technique can be applied “off-line” to validate the results obtained with our plan-based algorithm.
Our seed-based fusion technique, inspired by previous work [47, 48, 49], can be summarized in 5 steps:

1. Localization of the seed centroids on the TRUS images (figure 5–3)
2. Application of the ICP algorithm between the TRUS-based and the tomosynthesis-based seed positions.
3. One-to-one pairing of the TRUS-based and reconstructed seed positions.
4. Exclusion of pairs of points with a distance larger than 3 mm.
5. Re-application of the ICP algorithm with the remaining subset of points.

The localization of the seed centroids is performed on the SPOT PRO treatment planning system. Special care was taken to inspect the images in the vicinity of the planned seed position. Figure 5–3 presents a TRUS image, the planned seed positions and the manually identified seed positions for a patient implant. After the one-to-one pairing (step 3), all the pairs with a distance larger than 3 mm are discarded, because they are considered as false-positive manual seed identification. Plastic spacers, calcification, reconstruction artifacts or imprecise seed localization can lead to false-positive detections. After the exclusion of false-positives, an average of 10 seed positions (min = 6, max = 17) were fed into the ICP algorithm to find the final solid transformation. Figure 5–4 presents a standard match with very good agreement between the two subsets of points.

5.2 Results

For 17 patients, the tomosynthesis-based seed positions were first co-registered in the TRUS coordinate system with the seed-based method to get reference positions.
Figure 5–4: Co-registration between the TRUS-based seed positions (o) and the corresponding tomosynthesis-based seed positions (x) with the prostate contour.

Then, the difference between the plan-based method and the seed-based method were evaluated for validation purposes.

5.2.1 Registration error

As stated previously, the main restriction to the plan-based method is that it cannot handle a global shift between the planned and the real deposited seed positions. In other words, this means that the center of mass of the planned seed positions needs to be close to the center of mass of the real seed positions. To verify this, the seed-based co-registered seed positions were considered as the real seed positions and thus, the center of mass between this cloud of points and the planned cloud of points (Δx, Δy, Δz) could be evaluated (figure 5–5).
In most of the cases, the shift in the $x$ and $z$ are relatively small, with an average of the absolute difference under 2 mm in both directions. There is no significant systematic displacement in the $x$ or $z$ direction since the shifts can be either positive or negative. However, the $y$ direction, which is in the axis of needle implantation, presents a systematic shift with an average of 5.6 mm. Figure 5–6 shows that the planned seed positions are shifted toward the base of the prostate compared to the real deposited positions. This shift is clearly posing a problem with the plan-based co-registration method, since a small displacement of the target volume can lead to significant variation in the dosimetric coverage. The following section explores the impact of this shift on the dosimetric outcome.

5.2.2 Impact on prostate dosimetry

To evaluate the impact of the registration error that is associated with the plan-based co-registration technique, the dosimetry calculated with the plan-based method has been compared with the reference seed-based method. Since there is a significant shift between the planned and real position in the $y$ direction, one could expect significant discrepancies in the dosimetric parameters. Indeed, because of the rapid dose fall-off outside of the prostate boundary, small registration error can lead to large dosimetric uncertainty. The relative differences on the main dosimetric parameters, $D_{90}$ and $V_{100}$, are presented in figure 5–7. $D_{90}$ and $V_{100}$ are underestimated in most of the cases with the plan-based method. Furthermore, the differences are very large for many patients, in fact more than half of the cases presents a variation of $D_{90}$ larger than 10%. Such differences are unacceptable to evaluate accurately the dose given to the prostate.
Figure 5–5: Differences in $x$, $y$ and $z$ between the center of mass of the planned seed positions and of the co-registered seed positions with the seed-based method. The red dotted line is the mean value.
5.3 Discussion

First of all, the systematic shift in the $y$ direction needs to be analyzed to understand our further results. There can be two possible explanations to this apparent shift: (1) seeds are systematically, in the clinic, misplaced inside the prostate or (2) an error in the seed-based fusion generates this shift. Our seed-based fusion provides us with a very good match between the two clouds of points as one can see in figure 5–4. Consequently, the seed-based co-registration seems reliable in providing a precise fusion. However, it is not impossible that the SPOT PRO software mishandles the coordinate system displayed at the screen and generates the shift.

On the other hand, if our seed-based fusion is reliable and the seeds are really misplaced inside the prostate, several reasons could explain this systematic displacement. The most probable reason being the movement, stretching and deformation of the prostate soft tissue as a result of the needles insertion and retraction. Furthermore, this shift could also be caused by the suction effect of needle retraction [72]. Simulation studies have evaluated that the seeds could be misplaced by 20%
Figure 5–7: Relative difference on (a) $D_{90}$ and (b) $V_{100}$ of the plan-based vs the seed-based fusion. A positive value signifies that the plan-based parameter is larger.
of the width of the prostate due to soft tissue deformation [73]. In our case, the
displacement is in average 15% of the width of the prostate in a consistent direction
with the simulation results.

Assuming that the seed-based fusion is trustworthy, the plan-based fusion tech-
nique has shown to be imprecise on the main dosimetric parameters $D_{90}$ and $V_{100}$. Consequently, this method is unsuitable for precise postimplant intraoperative dose
evaluation. However further work has to be done to assess the uncertainty of our vali-
dation method, the seed-based fusion. The upcoming availability of a table mounted
stepper, in opposition with the floor mounted stepper clinically used, will help to
evaluate the precision of the seed placement inside the prostate and to elaborate an
effective fusion method. Indeed, the table mounted stepper offers the possibility to
image the seeds with the radiographs without taking out the TRUS probe. Thus,
direct co-registration between the two imaging modalities could be possible.
Chapter 6
Postimplant and Intraoperative Dosimetry: a Clinical Study

Although postimplant dosimetric analysis is common practice in prostate permanent implant, there are no clinical standards on how to perform it [74]. Since there is wide variation in the dosimetric information depending on the method [75], there is a real need for standardization of the postimplant procedure. The postimplant dosimetry analysis provides very useful information to identify possible sub-optimal dosimetric coverage, to help the physician improving his implant technique and to correlate the clinical outcomes to the quality of the implant.

One of the main challenges to evaluate the quality of an implant in LDR prostate brachytherapy is that the dose is inherently deposited dynamically over time. All the methods to assess the dosimetry only provide a snapshot of the dosimetric coverage at a single moment in time. However, the implant is not static over time, because the prostate size and shape are changing over the course of the treatment and the seeds can migrate through soft tissues or through the vascular system. Consequently, a significant uncertainty in postimplant dose evaluation comes from the generalization of an isolated observation over the entire life of the implant. If the postimplant dose evaluation is done too early after implantation while there can be severe edema, the dose delivered to the prostate may be underestimated. If the dose evaluation is done too late, the delivered dose may be underestimated. [76]. The optimum postimplant dosimetry timing varies for each patient, because it is dependent of the magnitude
and half-life of the edema. A study using a biomathematical model of prostate edema has shown that the mean percent difference in 80% coverage dose between the static model and the dynamic model is less than 5% when the postimplant dosimetry is evaluated during an optimum window of 4 to 10 weeks. However, this difference can go as high as 15% in cases with unusually long edema half-life and large edema magnitude [76]. Such a large difference between the static dosimetry and the dynamic dosimetry is unpredictable and can lead to significant under or over dosage of the prostate.

Thus, to achieve a very accurate dosimetry analysis, several postimplant dosimetry evaluation would have to be done over the life of the implant to limit these uncertainties. Because of prostate edema and of the higher dose rate at the beginning of the life of the implant, a special care would need to be taken to evaluate the dose deposited in the first few weeks. For instance, a sequence of dosimetry evaluation performed on day-0, day-14, day-30, day-60 and day-120 would allow to generate a very good picture of the real distribution of deposited radiation in the prostate. Figure 6–1 presents this proposed dose evaluation timing on the I-125 decay curve. However, such a longitudinal study would require a low cost, low dose and quick dosimetry analysis procedure, which is not available practically at the present time.

Nonetheless, the TRUS-based treatment planning, the tomosynthesis-based intraoperative analysis and the CT-based dosimetry provide information to investigate the evolution of the dosimetric coverage. Indeed, this 3-step dose coverage analysis reports the progression from the planning, the achieved dosimetry right after the implant to the dose coverage 1 month after the implant. The analysis of this information
is complex because the dose evaluations are based on different imaging modalities, which make them difficult to compare. Furthermore, prostate brachytherapy is very operator-dependent, so caution needs to be applied when attempting to generalize the dosimetric results obtained at the CHUM. Differences in patient selection, planning philosophy, and implant technique can lead to different outcomes from one institution to another. A total of 23 patients were included in this clinical dosimetry study that focuses mainly on the two most relevant dosimetric parameters, $D_{90}$ and $V_{100}$.

6.1 Dosimetry based only on reconstructed seed positions

The availability of the precise reconstructed seed positions can be used to generate and display the isodose distribution in axial plane or in 3D view. Even if the
tomosynthesis-based seed positions are not co-registered with the prostate and OAR contours, the dose coverage can still be evaluated in a qualitative manner. Based on the seed positioning, the dose coverage of the apex, mid gland and base can be displayed and inadequate dose coverage, such as gap, island or hole [77], can be identified. Figure 6–2 presents a patient case where a sub-optimal coverage can be visualized, even in the absence of the anatomical information. Indeed, the upper part of the mid gland region in figure 6–2(b) is clearly underdosed as shown by the 100% isodose gap (yellow line). In addition, cold spots can be suspected in the upper-center and lower-center part of the base in figure 6–2(c). However the prostate contours would be necessary, in this case, to draw a clear conclusion.

As presented in figure 6–2, a quick quality assessment can be done based on the seed distribution. This quick dose evaluation can even be used to re-implant additional seeds if isodose holes or islands are located within the seed cluster [77]. Despite the fact that the clinical team can have an approximate idea of the quality of the implant solely based on the seed positioning, the availability of the prostate boundary is crucial to compute relevant dosimetric parameters. Thus taking a clinical decision such as re-implanting additional seeds or giving an external beam radiation boost requires the precise localization of the anatomical structures in relation with the dose distribution.

6.2 TRUS-based dosimetry

The TRUS imaging provides dosimetric informations which are based on the initial treatment plan. The evolution of the TRUS-based dosimetry, over the course of the implantation, can be divided into the following three steps:
Figure 6–2: Isodose contours (80%, 100% and 150%) and seed positions (black diamonds) on axial slices located at the (a) apex, (b) mid gland and (c) base of the prostate.
1. Initial intraoperative treatment plan.

2. Initial plan corrected for needle placement with preimplant contour.

3. Initial plan corrected for needle placement with postimplant contour.

The difference between step 1 and 2 comes from the intraoperative manual correction of the needle placement based on the TRUS guidance. Approximately a third of the implanted needles are manually corrected by the medical physicists, because of obvious deviation from the planned positions. After the implantation, the physician delineates the prostate a final time to take into account the prostate displacement during the operation. Dosimetry calculation using the corrected seed positions and these postimplant contours is the most accurate dose analysis that can be provided using exclusively TRUS imaging. However, it is still imprecise because it relies on the treatment plan and does not take into account the real deposited seed positions.

The evolution of the dosimetric values, $D_{90}$ and $V_{100}$, in each of these three steps are presented in table 6–1. The correction of the needle position has very little influence over the $D_{90}$ and $V_{100}$ average values. However, when a large number of needles are corrected in a specific configuration, for instance all toward the center or the periphery of the prostate, then the dose distribution can be significantly affected. This can results either in larger or smaller parameter values. In 4 patients out of 23, the absolute differences in $D_{90}$ and $V_{100}$ were larger than respectively 10 Gy and 2%. As one could expect, using the postimplant instead of the preimplant contour has more influence on the dosimetry than small corrections in the needle placement. Indeed, the planned seed positions are optimized for the preimplant contour shape and positioning, and the dosimetric parameters are very sensitive to changes in the
target volume and position. In addition, an average increase of 4\% of the prostate volume is observable from the OR pre-plan to the OR post-plan volume, possibly due to prostate edema. Indeed, it is known that edema sets in very quickly as needles puncture the prostate. Thus, the longer the time between the two imaging sequences, the more discrepancy there will be between the OR post-plan and pre-plan. These reasons justify an average decrease between the initial and the final TRUS-based dosimetry of respectively 13.7 Gy and 3.1 \% on D\(_90\) and V\(_{100}\).

Table 6–1: Comparison between the different steps of the TRUS-based dosimetry analysis

<table>
<thead>
<tr>
<th></th>
<th>Initial intraoperative treatment plan</th>
<th>Initial plan corrected for needle placement with preimplant contour</th>
<th>Initial plan corrected for needle placement with postimplant contour</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(_90) (Gy)</td>
<td>159.8 ± 15.5</td>
<td>158.6 ± 14.0</td>
<td>146.1 ± 20.9</td>
</tr>
<tr>
<td>V(_{100}) (%)</td>
<td>93.6 ± 3.6</td>
<td>93.4 ± 3.3</td>
<td>90.5 ± 5.3</td>
</tr>
</tbody>
</table>

6.3 Postimplant dosimetry

Both postimplant intraoperative and day-30 CT-based dosimetry have significant uncertainties related to their respective imaging process. First, the intraoperative dosimetry is very sensitive to the precision of the co-registration between seeds and contour, but we cannot evaluate accurately the uncertainty of the seed-based fusion used in this dosimetric study. On the other hand, the CT-based dosimetry relies on user-dependent contouring of the prostate, which requires a certain amount
of subjectivity. From the literature, we could expect an increase in the prostate volume between day-0 TRUS contouring and day-30 CT contouring [22, 78, 79], but the opposite trend is observed at our institution. Actually an average diminution of 26% of the prostate volume was recorded between the two imaging sequences.

6.3.1 Intraoperative vs CT-based dose evaluation

One could expect that the postimplant dosimetry, either intraoperative or CT-based, would present poorer dosimetric values than the TRUS-based dosimetry corrected for needle placement with postimplant contour. In fact, this TRUS-based dosimetry approach is still based on the optimized planned seed configuration. Thus, using the real deposited seed positions should further decreased the quality of the dosimetric coverage. Results presented in table 6–2 show that this is true for the postimplant intraoperative dosimetry, but on the contrary the CT-based dosimetry presents better dosimetric values than the initial treatment plan. The CT-based analysis generates very good parameters, because the delineation of the gland excludes peripheral regions where the dose coverage could be problematic. This is another evidence that the CT-based dosimetry provides deficient information for postimplant dosimetry analysis.

In CT-based dosimetry, the main target is to obtain a $D_{90}$ value over the dose cutoff point fixed at 140 Gy. It has been reported that a PSA control rate of 68% is associated to a $D_{90} < 140$ Gy compared to a rate of 92% for $D_{90} > 140$ Gy [9]. However, it is not straight forward to apply this dose cutoff to the intraoperative
Table 6–2: Comparison between day-0 intraoperative dosimetry and day-30 computed tomography-based values with the TRUS-based postimplant dosimetry

<table>
<thead>
<tr>
<th></th>
<th>Initial plan corrected for needle placement with postimplant contour dosimetry</th>
<th>Postimplant intraoperative dosimetry</th>
<th>CT-based dosimetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D_{90}) (Gy)</td>
<td>146.1 ± 20.9</td>
<td>127 ± 18</td>
<td>164 ± 38</td>
</tr>
<tr>
<td>(V_{100}) (%)</td>
<td>90.5 ± 5.3</td>
<td>82 ± 8</td>
<td>93 ± 6</td>
</tr>
</tbody>
</table>

dosimetry since there is large variation in dose evaluation depending on the imaging modality. Figure 6–3 presents the absolute \(D_{90}\) values for CT-based and intraoperative dosimetry in relation with the 140 Gy dose cutoff. The vast majority of the patients have a CT-based \(D_{90}\) over or slightly under this cutoff. On the opposite, the intraoperative \(D_{90}\) is clearly deficient in relation to this criteria for most of the patients.

In conclusion, the seed-based intraoperative dosimetry presents more realistic values than the CT-based dosimetry, but it is still uncertain how accurate are these intraoperative values. However, it is probable that the introduction of a new standard in postimplant dosimetry evaluation should come with new dosimetric aims in terms of dosimetric parameters. Combining an accurate and reliable postimplant intraoperative dose assessment with new dosimetric standards, we believe that the day-30 CT-based dosimetry might become superfluous in the future. In fact, there is still a need for day-30 dosimetry, but the CT scan might be substitute for the intraoperative postimplant imaging methodology.
Figure 6–3: Seed-based intraoperative and CT-based D$_{90}$ for a sequence of patients. The red dotted line represents the D$_{90}$ dose cutoff for the CT-based postimplant dose analysis.
Chapter 7
Graphical User Interface

A graphical user interface has been developed with MATLAB® to provide visual feedback of all the steps leading to intraoperative dosimetric information. The GUI is composed of three modules corresponding to the three main steps of the postimplant intraoperative dosimetry assessment:

1. Input information and image processing,
2. Seed positioning display and correction,
3. Intraoperative dosimetric information.

7.1 Seed reconstruction input

The first window, presented in figure 7–1, allows the user to select the different parameters related to the seed reconstruction. First of all, the user needs to select the various files including the seven dicom images, the prostate contour, the organs-at-risk boundaries and the planned seed position. Then, the region-of-interest for each projection needs to be manually cropped to generate the seed-only images. After a ROI is selected, the result of the binarization is automatically displayed. Once the seven ROI have been selected, the user can come back to any image and re-crop a possibly misplaced ROI. Before proceeding to the tomosynthesis-based reconstruction, the user needs to specify the SAD for all projection orientations. Furthermore, for research purposes, the user can modify the resolution of the reconstructed volume, the threshold to generate the seed only volume and the minimum size of a
Figure 7–1: Initial module of the GUI window allowing the user to specify the various information necessary to the reconstruction.
cluster. Nevertheless, these values have already been optimized and should not be modified without a good reason. For instance, if a new type of seed with a different geometry is being introduced, there might be a need to modify the minimum size of a reconstructed seed. Finally, before proceeding to the reconstruction of the 3D seed position, the number of implanted seeds needs to be specified as an upper limit on the number of detected seeds.

7.2 Seed positioning correction

The main purpose of the second GUI window is to provide to the user a visual feedback of the reconstructed seed positions. As shown in figure 7–2, the 3D seed positions are projected on three displayed radiographs at different angles. One can choose to display any of the seven different projection angles that are used for the reconstruction. This allows the user to quickly identify potential major problem with the seed localization process. For instance, this could happen if the patient wakes up from anesthesia and moves during the radiography acquisition.

As was demonstrated in chapter 4, the completely automatic seed reconstruction process can provide adequate seed reconstruction, in most of the patient cases. However, this GUI window offers the possibility to correct possible seed localization flaws, either undetected or false-positive seeds. To delete a seed, one can simply push on the delete button and then click on the seed that needs to be deleted on the upper left figure. The 3-step procedure to add a seed is shown in figure 7–3. Basically, the user needs to select an undetected seed on the first projection (figure 7–2 upper-left), match it with a seed in the second projection (figure 7–2 lower-left) and confirm that the reconstructed position corresponds to an undetected seed in the third projection.
Figure 7–2: Second module of the GUI providing visual feedback of the seed localization and the possibility to add or delete seeds.
Figure 7–3: Process to add an undetected seed with the graphical user interface. (a) The line connecting the seed identified on projection 1 with its corresponding X-ray source is projected on image 2 to ease the identification of the corresponding seed. (b) The 3D seed position triangulated from projections 1 and 2 is projected on image 3 to validate the reconstruction.

To obtain the most accurate reconstruction, the angle between the first and the second projection should be as large as possible. With the possibility to scroll between seven projections, possible reconstruction errors can be easily identified and corrected. Two different users tested this GUI on 11 patients to correct for undetected seeds or false-positive detections. A mean time of 47 seconds was necessary to correct for approximately 3 errors per implant.

7.3 Dosimetric information display

Once the seed positioning corrections have been made with the second module, the dose distribution can be computed and displayed in the last GUI window. However, the dosimetry is generated with the plan-based method to perform the fusion
Figure 7–4: This module compiles in a single window all the main information necessary to evaluate the quality of the dosimetric coverage of the prostate.
with the prostate contour and organs-at-risk, which has shown to be an inappropriate method in chapter 5. Consequently the dosimetric information provided in this window is inaccurate and should not be taken as the absolute dosimetry. Still, this window could be easily modified to be used with an appropriate fusion technique.

The GUI presented in figure 7–4 includes all the important informations in a single window to assess the quality of the implant. The different components of this window are described below:

- **upper-left**: 3D visualization of the prostate, the planned seed position, the reconstructed seed position and the “slice of interest”,
- **upper-right**: isodose, prostate contour and reconstructed seed position for the “slice of interest”,
- **lower-left**: $D_{80}$, $D_{90}$, $D_{100}$, $V_{80}$, $V_{90}$, $V_{100}$, $V_{150}$, $V_{200}$ and prostate volume,
- **lower-right**: dose volume histogram.

Furthermore, a *cold spot visualizer* can provide a 3D representation of the possible zones of underdosage. First, a low-dose threshold is selected by the user and then the cold regions of the prostate are displayed in red as shown in figure 7–5. Finally, $D_2$ and $D_5$ of the urethra and the volume of the rectum wall receiving more than 144 Gy can be provided to evaluate the radiation impact on the organs-at-risk.
Figure 7–5: Cold spot visualizer: the prostate regions with a dose lower than the selected dose cutoff are displayed in red.
Chapter 8
Conclusions and Future Work

The classical procedure of the LDR prostate brachytherapy would benefit from an intraoperative postimplant dosimetry verification to allow the identification of possible sub-optimal dose coverage of the target. Several clinical factors influence the quality of an implant and many cases would benefit from the implantation of remedial seeds to correct for dosimetric flaws. Thus the clinical team would be confident that the prostate dose coverage is acceptable as the procedure is completed. The only significant dosimetric variability would then be related to prostate edema and seed migration.

The main objective of this project was to develop an efficient, operator-free, intraoperative dose evaluation technique using the imaging modalities commonly available in a brachytherapy treatment room. This would allow to discover any significant underdosage while the patient is still under anaesthesia in the treatment position. To achieve this specific aim, the 3D seed positions need to be reconstructed in relation to the prostate boundaries delineated with the transrectal ultrasound imaging capabilities. This project was divided into 3 principal steps: (1) tomosynthesis-based reconstruction of the seed positions, (2) co-registration with the prostate contour and (3) intraoperative dosimetry analysis.

(1) 3D seed positions. Our seed detection method involves a tomosynthesis-based reconstruction of the volume of interest. The seven projections required to
reconstruct the seed positions were acquired over an angle of 60° with an isocentric imaging system adjacent to the treatment table. Some image processing operations, based on mathematical morphology, were applied on each projection to efficiently and automatically segment the implanted seeds and to generate binary seed-only images. From these images, a binary seed-only volume was generated by backprojecting the seed-only images and applying a threshold on the reconstructed volume to segment the seeds. The seed positions were then retrieved with a 3D connected component analysis of the seed-only volume. A phantom study has demonstrated a sub-millimetric localization accuracy of 0.4 ± 0.4 mm. The reconstruction algorithm also provides the seed orientation with an uncertainty of 10° ± 8°. This enables us to achieve a more accurate dose calculation by including anisotropy effects. In a patient study with an average of 56 seeds per implant, the automatic tomosynthesis-based reconstruction yields a detection rate of 96.7% of the seeds and less than 2.6% of false-positives. This localization accuracy and the seed detection rate allow to generate an accurate dose distribution.

(2) Co-registration. The next objective is to co-register the prostate contour acquired with TRUS imaging with the tomosynthesis-based seed positions, which are two separate sets of coordinates. A method has been developed, a plan-based fusion, where the planned seed positions are used as the target points to match the reconstructed seed positions. An alternative method, a seed-based fusion, based on the localization of the seeds on the TRUS image has been developed to validate the plan-based method. Due to an average systematic shift of 5.6 mm between the
planned and the real deposited seed positions in the needle implantation axis, the plan-based fusion have shown to not be accurate enough for dose evaluation purposes.

(3) Dosimetry analysis. It has been shown that the 3D seed positions alone, without the anatomical information, could be used to localize possible cold spots. However, the seed-based method has been used to match the prostate contour with the seed positions to allow the precise evaluation of the target dosimetry. Comparing the planned and the postimplant intraoperative dosimetry, an average decrease of 20% of the D$_{90}$ was observed. In addition, the comparison of the intraoperative and the day-30 CT-based dosimetry has raised serious doubt on the capacity of computed tomography to provide trustworthy dosimetric parameters.

Finally, a graphical user interface has been developed to link all the different components of this project into a user-friendly software. This GUI is composed of 3 modules to provide visual feedback of the image processing, the reconstructed seed positions, and the main dosimetric indicators.

8.1 Future directions

One of the main challenge of intraoperative dosimetry is to limit the additional time needed to complete the procedure, since the whole clinical team has to wait for these results. Our tomosynthesis-based seed reconstruction method is very beneficial in this aspect. As shown in table 8–1, the actual method implemented at the CHUM can be performed in an average time of 7 to 8 minutes. This is fairly reasonable in comparison to the 90 to 120 minutes needed to complete the procedure. However, the total time of the procedure could be further reduced with by automating the image acquisition system and by implementing the reconstruction algorithm on a
streaming architecture platform (GPUs). These future enhancements should reduce the additional time to a total of 2 to 3 minutes (table 8–1).

Table 8–1: Average additional time to reconstruct the 3D seed position.

<table>
<thead>
<tr>
<th></th>
<th>Actual tomosynthesis-based method</th>
<th>Optimised tomosynthesis-based method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image acquisition</td>
<td>300 s</td>
<td>5 s</td>
</tr>
<tr>
<td>Image processing</td>
<td>60 s</td>
<td>60 s</td>
</tr>
<tr>
<td>Seed position reconstruction</td>
<td>30 s</td>
<td>2-3 s</td>
</tr>
<tr>
<td>Manual seed correction</td>
<td>0-120 s</td>
<td>0-120 s</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7-8 min</strong></td>
<td><strong>2-3 min</strong></td>
</tr>
</tbody>
</table>

An efficient, quick and accurate co-registration method still needs to be developed to merge the TRUS-based anatomical structures with the 3D seed positions. For this purpose, a table mounted stepper could be used to dynamically image the organs and the seeds, while the patient is still in lithotomical position. A limited angle seed reconstruction method is ideal in this situation, because the rotation of the simulator is physically limited by the patient’s position. As an alternative method for seed detection, the possibility of a full CBCT or a continuous low dose acquisition between -30° et 30° should be explored. To further refine the dosimetric calculation, a mathematical model of soft tissue deformation could be developed to compensate for the pressure of the TRUS probe and to take into account prostate edema.

Finally, even with perfectly registered seed positions and organ boundaries, a paradigm shift concerning dose calculation is desirable. The actual TG-43 formalism neglects the interseed attenuation and the effect of tissue heterogeneities, which can
result in large differences in absolute dosimetry. A Monte Carlo dose calculation engine could take into account these effects with the availability of CT imaging. Another paradigm shift concerns the generalization of a single postimplant dose evaluation to the lifetime of the implant. The accuracy of the dose evaluation would benefit from several postimplant dose evaluation acquired at different moment over the lifetime of the implant.

We believe that enhancements in intraoperative dose evaluation will ultimately set new standards in the quality of prostate brachytherapy. The next generation of clinical brachytherapy systems will probably include intraoperative dosimetric capabilities. This procedure will provide guidance to achieve better dose distributions which should result in better clinical outcomes. However, great care needs to be taken not to overdose the rectum and the urethra which has shown to affect the quality of life of the patient. Furthermore, such a procedure involves giving an additional dose resulting from the radiographs to the patient, but this X-ray dose is fairly moderate compared to the treatment dose. As the implant quality specifiers will refine, it is clear that the postimplant intraoperative evaluation will become more and more profitable for brachytherapists.
REFERENCES


KEY TO ABBREVIATIONS

PSA: Prostate-Specific Antigen
EBRT: External Beam Radiotherapy
LDR: Low Dose Rate
HDR: High Dose Rate
TRUS: Transrectal Ultrasound
I-125: Iodine 125
Pd-103: Palladium 103
OR: Operating Room
CHUM: Centre Hospitalier de l’Université de Montréal
AAPM: American Association of Physicists in Medicine
TG-43: Task Group No. 43
TG-64: Task Group No. 64
3D: 3 Dimensional
2D: 2 Dimensional
ABS: American Brachytherapy Society
CT: Computed Tomography
MRI: Magnetic Resonance Imaging
NP-hard: Nondeterministic Polynomial-time hard
DTS: Digital Tomosynthesis
CBCT: Cone-Beam Computed Tomography
SAD: Source-to-Axis Distance
SDD: Source-to-Detector Distance
**ICP:** Iterative Closest Point

**GUI:** Graphical User Interface

**OAR:** Organ-At-Risk

**ROI:** Region-Of-Interest

**GPU:** Graphics Processing Unit