INTRAOPERATIVE USE OF C-ARM CONE BEAM CT FOR QUALITY ASSURANCE OF LOW DOSE RATE PROSTATE BRACHYTHERAPY DOSE DELIVERY

by

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Abstract

Prostate cancer is the most diagnosed cancer among men. Many patients with localized prostate cancer are treated with brachytherapy, one form of which involves permanent implantation of approximately 100 radioactive sources into and sometimes immediately around the prostate while the patient is anesthetized. During the procedure, transrectal ultrasound (TRUS) and fluoroscopic images (acquired using a mobile C-arm fluoroscopic X-ray system) are used to guide and visually assess implant quality, but do not provide accurate quantitative dosimetry. Thus, the patient undergoes a CT scan after the implantation is completed for dosimetric evaluation. However, this practice is not ideal as it occurs after the patient has left the operating room, when there is no longer any opportunity to modify the implant, if required.

In this research project, a workflow was developed to assess the feasibility of performing intraoperative dosimetry using two routinely available imaging systems (a cone beam CT (CBCT) capable C-arm, and an ultrasound machine) for intraoperative dosimetric assessment of permanent implant prostate brachytherapy. In the proposed methods, the locations of all implanted sources were obtained from either 3D reconstructions of multiple planar radiographs, or from CBCT images. They were then registered to prostate contours delineated on the TRUS images, based on a common subset of sources identified on both image sets. In this process, prostate contours were deformed, using a finite element model, to take into account the effect of probe pressure in the TRUS images. Prostate dosimetric parameters obtained using this method were in agreement with postimplant CT dosimetry results, considering the uncertainty associated with each of these methods.
An algorithm for automatic detection of seeds on TRUS images using a convolutional neural network was also developed during the course of this work. The model was trained to detect the needle track first and then the individual sources within the needle track. This automated approach outperformed a human observer in precision.

The results of the work described in this thesis support the conclusion that the proposed dosimetry methods are feasible for real-time intraoperative dosimetric analysis of the implant and can potentially also replace postimplant CT dosimetry.
Lay Summary

Prostate cancer is one of the most common types of cancer in men. One of the approaches for prostate cancer treatment is brachytherapy, which is an internal form of radiation therapy. In this method, radiation is delivered to the tumor by placing radioactive sources either inside or near the tumor. In the operating room, ultrasound and X-ray imaging are used to guide the placement of the sources. However, these imaging methods are individually limited in providing sufficient information to fully assess the quality of the implant. Thus, in current practice, implant quality is assessed after the procedure and outside the operating room by taking a CT scan of the pelvis area. In this thesis, a workflow was developed to assess the quality of the brachytherapy implant by combining the information from ultrasound and X-ray imaging that are available in the operating room. As a result, the physician can make necessary adjustments to the treatment plan while the patient is still on the operating table, therefore improving the quality of the implant.
Preface

A version of chapter 2 has been presented as a poster in the 63rd annual scientific meeting of the Canadian Organization of Medical Physicists (COMP). The study performed in this chapter was approved by the University of British Columbia Research Ethics Board (certificate number: H12-03229).

The results from chapter 3 have been orally presented in the COMP 63rd annual scientific meeting and the 2018 World Congress on Medical Physics & Biomedical Engineering. A version of chapter 3 has been published in the Brachytherapy journal.


I conducted and coordinated all stages of this study including the University of British Columbia Research Ethics Board submission preparation (certificate number: H14-02658), patient recruitment (under the supervision of the physician and principal investigator, Dr. Michael Peacock), data collection in the operating room and data analysis. (These data were used for the work described in both chapters 3 and 4).

I completed the research described in chapter 3 under the main supervision of Dr. Ingrid Spadinger and co-supervision of Dr. Septimiu E Salcudean and Dr. Sara Mahdavi, who provided research guidance and technical support and advice. Dr. Mahdavi assisted in the data collection
as well. Dr. James Morris provided clinical expertise and was the initial principal investigator of the clinical study. Dr. Tom Pickles provided clinical advice and support at all stages of the study. Dr. James Morris, Dr. Mira Keyes and Dr. Michael Peacock contoured the prostate boundary on ultrasound and CT images of the study patients. Dr. Golnoosh Samei developed the finite element model that is used for deformation of the prostate contour.

A version of chapter 4 has been published in the Physics in Medicine and Biology journal.


I am the first and corresponding author of this research. I completed this research under the main supervision of Dr. Spadinger and co-supervision of Dr. Mahdavi, who provided research guidance and advice. Dr. Salcudean suggested the idea of applying an object detection convolutional neural network (CNN) tool to the radiofrequency ultrasound signal for detection of brachytherapy seeds. Dr. Davood Karimi provided the technical support of the CNN model. Julio Lobo helped with the 3D ultrasound data acquisition in the operating room. I carried out all the data analysis and developed the algorithm for seed detection on ultrasound images. I wrote most of the manuscript but Dr. Spadinger, Dr. Mahdavi and Dr. Karimi actively participated in editing and revising the manuscript for publication.
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<th>Description</th>
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<tr>
<td>1D</td>
<td>One Dimensional</td>
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<tr>
<td>2D</td>
<td>Two Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
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<tr>
<td>CBCT</td>
<td>Cone Beam Computed Tomography</td>
</tr>
<tr>
<td>cc</td>
<td>cubic centimeter</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CNN</td>
<td>Convolutional Neural Network</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
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<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
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<tr>
<td>FEM</td>
<td>Finite Element Model</td>
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<tr>
<td>HIFU</td>
<td>High Intensity Focused Ultrasound</td>
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<tr>
<td>LDR</td>
<td>Low Dose Rate</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>OAR</td>
<td>Organs at Risk</td>
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<tr>
<td>OR</td>
<td>Operating Room</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PIPB</td>
<td>Permanent Implant Prostate Brachytherapy</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<tr>
<td>PSMA</td>
<td>Prostate Specific Membrane Antigen</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
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<tr>
<td>ReLU</td>
<td>Rectified Linear Unit</td>
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<td>Treatment Planning System</td>
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<tr>
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<td>Transrectal Ultrasound</td>
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To Maman and Baba

Who have always encouraged me to go on every adventure especially this one
Chapter 1: Introduction

1.1 Clinical Background

1.1.1 Prostate Anatomy

The prostate gland is part of the male reproductive and urinary system and contributes to the production of seminal fluid. The normal adult prostate gland is about the size of a walnut, but tends to grow larger with age when men reach their 50s. It is located anterior to the rectum and inferior to the urinary bladder, and surrounds part of the urethra. The superior aspect of the prostate is referred to as the base, and the inferior aspect as the apex. The bladder neck often protrudes into the anterior base of the prostate as it transitions into the prostatic urethra, and the prostate gland blends into the musculature of the pelvic floor in the apex. Seminal vesicles are glands that make most of the fluid in semen and lie on the superior posterior aspect of the gland. A sagittal view of the prostate anatomy is shown in Figure 1.1.

Figure 1.1: A sagittal view of the prostate anatomy
1.1.2 Incidence and Diagnosis of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men, with increasing incidence in older age groups. Based on the most recent data available from the Canadian Cancer Society [1], 1 in 9 males is expected to be diagnosed with prostate cancer in their lifetime and it is the third most common cause of cancer death among Canadian men. The estimated numbers of new cases to be diagnosed with prostate cancer in Canada were 22,900 in 2019 [1] and 23,300 in 2020 [2].

Common prostate cancer diagnosis methods are screening of serum prostate specific antigen (PSA) levels and digital rectal examination (DRE). PSA is a protein secreted by the epithelial cells of the prostate gland. It is a component of the semen, where it acts as a liquefier, and can also be found in the blood. Typically, cancerous prostate glands release more PSA into the blood circulation than healthy prostate glands. The PSA level is determined from a blood test and is reported as nanograms of PSA per millimeter (ng/mL) of blood. Normal PSA ranges are age-specific and will increase with age. DRE is performed by the physician to detect prostate abnormalities by feel. If there is a high PSA level or a lump is felt during DRE, confirmation of cancer can be obtained by pathologic examination of prostate tissue biopsies. If cancer is found, it will be assigned a stage and grade. Risk assessment of the cancer is then performed by physicians to help them in recommending the type of therapy for treating the cancer.

1.1.3 Cancer Stage and Risk Grouping

The grade of a cancer is a qualitative assessment of the degree of differentiation of the tumor. Grade may reflect the extent to which a tumor resembles the normal tissue at that site and determines the aggressiveness of the cancer. The recommended grading system for prostate
cancer is the Gleason Grading system, which is obtained based on a histologic scoring of the patterns observed in the biopsy samples. Five basic grade patterns are used to generate a histologic score, which can range from 2 to 10, by adding the primary grade pattern and the secondary grade pattern [3]. High Gleason score means the cancer tissue is very different from normal and the tumor is more likely to spread.

Clinical staging of prostate cancer determines the extent of disease by incorporating information from symptoms, physical examination and biopsy results. The most clinically useful staging system is the TNM system, promulgated by the American Joint Committee on Cancer [4], [5], which classifies cancers by the size and extent of the primary tumor (T), involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M). For each of T, N and M the use of increasing values (T1, T2, T3 and T4) shows progressively greater extent of the cancer. In addition to primary tumor basic categories, sub-categories such as T2a, T2b and T2c may be used to add more description. All this information is combined, along with Gleason score and PSA level, in a process called stage grouping. Four stages are defined for prostate cancer which are expressed in Roman numerals from I to IV. In stage I, cancer is localized and is found in the prostate only. In stage II, the tumor has grown inside the prostate but has not extended beyond it. In stage III, cancer has spread beyond the outer layer of the prostate and may have spread to the seminal vesicles. In stage IV, cancer has metastasized to other tissues.

To assist in therapeutic treatment decision-making, it is critical to use accepted prostate cancer risk-stratification. A combination of prognostic factors including biopsy Gleason score, PSA level and clinical stage are used to determine different risk classifications. National
Comprehensive Cancer Network [6] guidelines currently include the following three group classifications:

Low risk: Gleason score \( \leq 6 \), and PSA < 10 ng/mL, and clinical tumor classification, T1, T2a.

Intermediate risk: Gleason score 7, or PSA > 10 ng/mL but < 20 ng/mL, or clinical tumor classification of T2b, T2c.

High risk: Gleason score 8-10, or PSA > 20 ng/mL, or clinical tumor classification of T3a.

1.1.4 Imaging Modalities Used in Prostate Cancer Management

Imaging technology is increasingly used to help with detection, localization and treatment of prostate cancer. Current, commonly used imaging modalities for management of prostate cancer include Magnetic Resonance Imaging (MRI), ultrasound, Computed Tomography (CT) and Positron Emission Tomography (PET).

1.1.4.1 MRI

Magnetic resonance images are derived from signals produced by hydrogen nuclei in the presence of specifically configured static magnetic fields and radiofrequency waves. Water is by far the most abundant molecule in the human body, and since each water molecule consists of one oxygen atom and two hydrogen nuclei, most of the signal originates from these molecules.

Each proton in the hydrogen nucleus has spin angular momentum, and since it is charged, it has a net magnetic moment. In the absence of an external magnetic field, the magnetic moments of a collection of protons will be oriented randomly. In the presence of an external magnetic field, some of the moments align in the same direction as the external field ("parallel"), while others
point in the opposite direction ("anti-parallel"). The energy associated with the parallel state is slightly lower than the energy associated with the antiparallel state. Therefore, the parallel state will preferentially be occupied and there will be a net longitudinal component of magnetization, $M_{0z}$, in the direction of the external magnetic field (usually defined as being along the Z-axis).

Besides the longitudinal component parallel to the applied magnetic field, there are also transverse components orthogonal to the direction of the applied field. Due to the interaction of the magnetic moment and field, the transverse components precess around the magnetic field vector. The frequency of precession is known as the Larmor frequency, $\omega_0$, and is given by:

$$\omega_0 = \gamma B_0$$  \hspace{1cm} (1.1)

where $\gamma$ is the gyromagnetic ratio of the proton and $B_0$ is the magnetic field strength. Because the transverse components of the protons are out of phase, the net transverse magnetization is nevertheless zero.

The net magnetic moment $M_0$, which is the summation of all individual magnetic moments present in the hydrogen nuclei, depends on the total number of protons in the volume as well as the temperature. $M_0$ is many orders of magnitude smaller than the external magnetic field and therefore it cannot be measured when it is aligned with the external magnetic field ($B_0$). In order to obtain a measurable signal, an additional magnetic field ($B_1$) in the form of an electromagnetic wave pulse is applied to the system. The frequency of this pulse is chosen to match the Larmor
frequency - i.e. it is resonant with the frequency of the spin precession. Since the Larmor frequency is typically in the RF range, this process is often called an RF excitation.

If the RF pulse is oriented in a direction perpendicular to the main magnetic field, it causes the precessing transverse components to become synchronized, creating a detectable transverse signal. The net longitudinal component of magnetization (M₀z) is also affected by the pulse. Both effects gradually diminish, where the rate of decay is affected by the interaction of hydrogen nuclei with the surrounding environment (spin-lattice) as well the neighbouring nuclei (spin-spin).

Spin-spin relaxation is the phenomenon that causes the disappearance of the transverse component of the net magnetization vector. This process is called free induction decay. Physically, each spin vector experiences a net magnetic field that depends on its chemical environment, and the rate at which the transverse components of the spins return to being out of phase depends on this. This rate is characterized by an exponential decay process with a time constant (T₂) that depends considerably on the tissue composition.

Spin-lattice relaxation is the phenomenon that causes the longitudinal component of the net magnetization vector to return to the value it had prior to being disturbed by the RF pulse. In this process, energy is transferred to the surrounding macromolecules (lattice), causing increased vibration of the lattice molecules, which is then transformed into heat. Over time, the spins are returned to their preferred state and the longitudinal component of the net magnetization returns to its equilibrium value. Mathematically, longitudinal relaxation is modelled by an exponential
growth function which is characterized by the relaxation time constant $T_1$, which, like $T_2$, depends on the tissue type. Because it involves the longitudinal field component, $T_1$ cannot be measured directly. An indirect process that involves tipping the longitudinal magnetization vector into the X-Y plane is therefore used. Proton density, $T_1$ and $T_2$ time constants vary between different tissues, which enables MRI to offer the possibility of obtaining high contrast between different soft tissues.

In order to localize the spatial origin of the MR signal, an additional non-uniform magnetic field that changes linearly in the desired direction is generated by a series of coils called gradient coils. Considering that Larmor frequency is linearly related to the magnitude of the static magnetic field and excitation of spins happen when the frequency of the applied RF pulse matches the Larmor frequency of the static magnetic field, a non-uniform magnetic field causes a given RF signal to excite only spins within a limited volume of the sample, and therefore the detected signal can be spatially localized. If the gradient is in the z-direction, this technique is called slice selection and discriminates spin locations along the patient’s superior-inferior axis (Z-axis). In order to localize the signal in the other two planes, frequency encoding or phase encoding is performed.

In the frequency encoding technique, another non-uniform magnetic field is applied in one of the other two coordinates. For example, if the non-uniform magnetic field varies in the X-direction, the spins along the X-axis are going to precess at different Larmor frequencies. Fourier analysis can be used to separate out the frequencies in the detected signal and associate them with a spatial coordinate along the gradient axis.
To complete spatial localization, another technique must be used to discriminate spins at different locations along the third dimension. The signal produced from the free induction process contains information about both the magnitude and phase of the magnetization vectors. In the phase encoding technique, a non-uniform magnetic field which varies linearly in the Y-direction is applied for a short period of time between slice selection and frequency encoding. This causes the nuclei at different positions along the Y-axis to have different initial phases, and nuclei at different positions along the X-axis to precess with different Larmor frequencies. 2D fourier transformation can be applied to the detected signals to form MR images.

MRI provides superb soft tissue contrast, and is therefore the ideal modality for prostate visualization. MRI shows in detail the internal prostatic anatomy and prostatic margins, and can be used for diagnosis and treatment planning of prostate cancer. MRI is considered by many researchers as the gold standard for prostate delineation [7]. MRI-ultrasound fusion and MRI-CT fusion can assist in prostate delineation on ultrasound and CT images, respectively, for management of prostate cancer. However, MRI is expensive and not available everywhere.

1.1.4.2 Ultrasound

Ultrasound imaging is the oldest and most widely used technique for visualization of the prostate, and is used in clinical management of prostate cancer. In this imaging modality, sound pulses are directed into the body using an ultrasound transducer, which converts electrical signals into sound waves using a piezoelectric crystal and a principle called the piezoelectric (pressure electricity) effect. A sound wave travels inside the tissue until it hits an interface between two tissues with different acoustic properties. Some proportion of the incident wave is reflected at the
boundary and some portion of it is transmitted. The reflected waves are picked up by the ultrasound transducer and converted back into electrical signals that are processed to create images.

Due to the conversion of acoustic energy into heat in the propagating sound wave, it also loses energy while travelling inside the tissue. This is referred to as attenuation. It causes an exponential decay of the amplitude of the travelling wave and therefore limits the depth to which image formation is possible.

Ultrasound wave reflection at a tissue boundary happens due to the differences in tissue density and elasticity, which affect the speed of sound (c) in the tissue. In solid materials:

\[
c = \frac{V}{\sqrt{\rho}}
\]  

(1.2)

where \( c \) is the ultrasound wave velocity in the medium, \( V \) is Young's modulus (which describes the relative stiffness of a material), and \( \rho \) is the mass density.

Wave propagation through any homogenous medium is characterized by its specific acoustic impedance \( Z \). Acoustic impedance is a measure of resistance to the passage of sound waves:

\[
z = \rho \cdot c = \sqrt{\rho V}
\]  

(1.3)
The amount of ultrasound reflected at a tissue interface depends on the acoustic impedance mismatch between the tissues. For example, most of the ultrasound energy will be reflected at interfaces where there are large density differences, such as a large pocket of gas or solid material in the tissue. No image information can be obtained from the region beyond such interfaces.

At interfaces where the waves are partially transmitted through the boundary, they do not always propagate in the same direction as the incident wave. This interaction is referred to as refraction. The refracted waves can travel further until they are either fully attenuated or reach additional boundaries and interact with them.

The reflected waves received by the ultrasound transducer are converted into an electrical signal. These raw data are referred to as radiofrequency (RF) data. For 2D image display (called B-mode), the amplitude of the returned echo signal is displayed as brightness, and pixel depth is determined from the time taken to receive the echo. The best images for visualization are produced by non-linear mapping of the raw RF signal amplitudes to the image gray scale. Logarithmic compression is typically used for this purpose.

The most common ultrasound imaging technique for prostate visualization is grayscale B-mode transrectal ultrasound (TRUS) imaging. The transducer used for prostate visualization is a biplane transducer and allows imaging in the axial plane as well as the sagittal plane, without changing the orientation of the transducer. This transducer, which is usually referred to as a
probe, is inserted into the patient’s rectum during imaging. Ultrasound imaging is safe, inexpensive and widely available, and provides real-time images, with high soft tissue contrast.

1.1.4.3 CT

In CT imaging, the patient is exposed to highly collimated X-ray beams with a spectrum of photon energies that typically ranges from about 10 keV to 150 keV. When an X-ray beam passes through a material of thickness \( d \), the intensity of the outgoing beam \( I_{out} \) is related to the intensity of incoming beam \( I_{in} \) by:

\[
I_{out} = I_{in} e^{-\mu d}
\]

(1.4)

where \( \mu \) is called the linear attenuation coefficient (typically expressed in cm\(^{-1}\)) and is a function of photon energy, material composition, and material density.

When photons travel through an absorber, they can undergo different types of interactions, with relative probabilities depending on the photon energy (which ranges over a spectrum for X-ray beams) and the material composition. X-rays are ionizing waves, which means that X-ray photons have enough energy to eject an electron from the atom. In the range of diagnostic X-ray beam energies, the primary interactions that take place are Compton (incoherent) scattering and photoelectric effect.

In Compton scattering, the photon collides with a loosely bound (i.e. with negligible binding energy) outer shell electron of an atom. The incident photon loses energy to the electron, which
is set into motion. In this process, the photon is scattered at an angle different from its original direction. Compton scattering is undesirable in diagnostic X-ray imaging, since the scattered photons resulting from Compton interactions can reach the image receptor and decrease the contrast of the image.

In the photoelectric effect, the photon collides with an atom and causes the ejection of a bound electron. All the photon energy is transferred to the ejected electron, which is therefore called a photoelectron. Some of the photon’s energy is used to overcome the binding energy of the shell from which the electron is ejected, and the rest of the photon’s energy is given to the electron as kinetic energy. Photoelectric effect is highly dependent on the atomic number (Z) of the target atom and the probability of interaction is proportional to Z³ for photons in the diagnostic energy range. However, the probability of photoelectric effect diminishes rapidly (in proportion to 1/E³) with increasing photon energy. In contrast, the probability of Compton interactions taking place is proportional to the electron density of the material, and increases with energy.

The relatively high proportion of photoelectric events at diagnostic energies contributes to good contrast between tissues with different atomic number compositions, such as bone (effective Z≈14) and soft tissue (effective Z≈7). Because the linear attenuation coefficient, which represents all interactions taking place, also depends on the material density, good contrast between tissues of different densities, such as lung and soft tissue or bone, is also achieved.

Conventional CT scanners acquire a series of thin cross-sectional images of the body by exposing the patient to a highly collimated X-ray beam. The X-ray source performs a continuous
series of 360 degree rotations around the body, as the patient is translated relative to the imaging system, to produce a series of axial image slices. Most CT scanners use a fan beam, and at multiple directions of the beam as the X-ray source rotates, the X-ray absorption pattern is recorded by a linear or arced array of detectors located on the opposite side of the patient. The detectors also have collimators placed in front of them to reduce the amount of out-of-slice scattered radiation reaching them.

An alternative mode of CT image acquisition is cone beam CT (CBCT), where projections from a single full or partial rotation of a broad X-ray beam are captured by a large flat panel digital detector.

The standard method of reconstructing the CT image in each slice is backprojection. In this process, the attenuation profiles acquired from the different views (angles) around the patient are projected (“smeared”) back towards the source position through the axial image plane. Superposition of the projections obtained at different angles creates the image. Backprojection is efficient and involves relatively simple calculations, but the resulting images are blurry. To reduce this blur, a filter function is mathematically applied to each view before projection. The mathematical operation is called convolution, but the reconstruction method is referred to as filtered back projection. Most CT scanners offer a choice of filters to enhance either soft tissue features or bone detail in the images.

Iterative reconstruction is another technique that is used for image reconstruction. In this method, an initial image guess is made and then refined over several tries. The result of these iterative
reconstruction processes is improved image quality, in terms of spatial resolution and reduction of noise and reconstruction artifacts. However, it is computationally more intensive than backprojection and therefore requires more time to obtain the images.

In modern CT scanners, the images consist of $512 \times 512$ pixels representing the CT number, which is expressed in Hounsfield units (HU). The CT number is defined as:

$$HU = 1000 \left( \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}}} \right)$$

(1.5)

where $\mu$ and $\mu_{\text{water}}$ are the linear attenuation coefficients for the tissue material and for water, respectively. As mentioned before, $\mu$ depends on material composition and density, as well as the energy of the absorbed X-rays. In the HU definition, the CT number of air and water are $-1000$ HU and 0 HU, respectively. The image derived from the HU values is displayed as a gray scale. Usually, the highest number is assigned to white and the lowest number to black, with all intermediate numbers assigned intensities on a linear scale.

CT imaging does not produce good soft tissue contrast and cannot provide details about the structure of soft tissue, so it cannot be used for prostate cancer diagnosis; however, it can be used for planning and assessment of some prostate cancer treatments where the overall shape and boundary of the prostate is needed. Nevertheless, the delineated volume is likely to be imprecise as it can be difficult to distinguish the prostate from the surrounding structures.
1.1.4.4 PET

PET is an example of nuclear medicine imaging. In this type of imaging, radiopharmaceuticals (or radiotracers) are administered to the patient through injection prior to the imaging scan. The tracer is distributed by the bloodstream and the tracer molecules accumulate in organs and tissues of interest according to their biochemical properties. Radioactive isotopes (in particular, positron emitters with relatively short half-lives) incorporated into the tracers undergo decay, and their decay products are the basis of PET imaging. Specifically, a proton within the atomic nucleus of the radionuclide is transformed essentially into a neutron (n) and a positron (e⁺):

\[
\frac{A}{z}X \rightarrow z-1Y + e^+ \\
p^+ \rightarrow n + e^+
\]  

(1.6)

where X and Y represent different elements. The emitted positron has some kinetic energy, which it loses via Coulomb interactions with the surrounding electrons in the medium. After travelling a short distance (1–10 mm) in the tissues, the positron interacts with an electron in the medium, and both particles are annihilated. Each annihilation reaction results in the emission of two gamma rays (photons) with energy 511 KeV (which is equivalent to rest mass of the annihilated electron or positron) in roughly opposite directions from the point of annihilation.

These two gamma photons are detected by one or more rings of scintillation detectors encircling the patient. Whenever two opposite detectors register a gamma photon at nearly the same time, the system records a coincidence event which indicates that the gamma photons could have originated from the same electron-positron annihilation. The recorded coincidence events are then used to reconstruct an image of the radiotracer distribution.
PET imaging is used in the diagnosis and localization of prostate cancer. With suitable radiotracers, PET imaging can highlight the metabolic, molecular or cellular activity of prostate cells and is used in conjunction with anatomical imaging in the form of PET/MRI or PET/CT [8].

In recent years, prostate-specific membrane antigen (PSMA), which is highly expressed on the membranes of prostate cancer cells, has gained popularity as a biomarker in prostate cancer diagnosis. PSMA specific radiotracers bind to the PSMA antigen, and include 2-(3-(1-carboxy-5-[(6-[18F] fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (18F-DCFPyL) and Gallium-68 (68Ga)-PSMA ligand (68Ga-PSMA). They are low-molecular-weight agents and have shown high uptake in tumor foci [9], which can be used for diagnosis of cancer relapse and also assist in TNM staging of the prostate cancer [10] and delineation of the primary tumor [11].

1.1.5 Prostate Cancer Treatment Options

Treatment options for prostate cancer depend on the type and stage of the cancer as well as the patient’s preferences and overall health. Current common treatment options for early stage prostate cancer include active surveillance, hormone therapy, prostatectomy, and radiation therapy.

Active surveillance involves frequent monitoring of the tumor using a combination of DREs, PSA tests and biopsy results. No treatment is given to a patient unless there are significant changes in test results. Hormone therapy is a treatment based on the suppression of naturally present androgen hormones that stimulate prostate cancer cells to grow. Hormone therapy may
be used alone as a main treatment or along with other treatments to shrink the tumor. Hormone therapy for prostate cancer is also known as androgen deprivation therapy. Radical prostatectomy is the surgical removal of the entire prostate and seminal vesicles and, in some cases, lymph nodes in the pelvic area.

Radiation therapy is the use of ionizing radiation to kill cancer cells or stop them from growing and can be delivered externally or internally. External beam radiotherapy refers to treatment techniques where a particle accelerator based treatment unit is used to generate and direct a radiation beam (such as an X-ray or proton beam) from different directions to the area with cancer. Internal radiotherapy refers to radiation therapy techniques where radioactive sources are implanted inside and immediately adjacent to the tumor to deliver radiation at a short distance. This technique is known as brachytherapy, derived from the Greek term “brakhus” or “brachy” meaning “short”. There are two categories of brachytherapy in terms of implant duration: permanent and temporary, both of which are options for prostate cancer treatment.

In temporary brachytherapy, the radioactive material is temporarily introduced into or close to the tumor and is removed once the desired radiation dose has been delivered. Most temporary procedures are delivered using remote after loading machines, where hollow needles, catheters or other types of applicators are first inserted into the target volume by the physician. After insertion is completed, the applicator positions are confirmed using a diagnostic imaging modality such as planar radiographs, CT, MRI, or ultrasound (CT being the most common), and a treatment plan specifying the distribution of radioactivity is finalized on the basis of this information. The radioactive material is then introduced into the applicators according to the
treatment plan by a computer-controlled device that drives a single high dose rate (HDR) source
\((^{192}\text{Ir} \text{ or } ^{60}\text{Co})\) to a series of sequential positions inside the applicators. The time spent by the
source at each position is on the order of a few seconds, and is specified by the treatment plan.

In permanent brachytherapy, low dose rate (LDR) radioactive sources are permanently implanted
into the tissue by the physician. Radionuclides favoured for permanent implant have a relatively
short half-life, and low energy photon emissions. Examples include \(^{125}\text{I}\) with a half-life of 59.4
days, \(^{103}\text{Pd}\) with a half-life of 17 days and \(^{131}\text{Cs}\) with a half-life of 9.7 days. In the context of
prostate cancer, LDR brachytherapy is usually referred to as permanent implant prostate
brachytherapy (PIPB).

Surgery and radiation therapy are the standard treatments for localized prostate cancer; however,
some patients with high-risk cancer may benefit from multi-modality approaches. For example,
post-prostatectomy radiotherapy may be considered for patients with high-risk cancer based on
pathologic features from prostatectomy, or addition of brachytherapy boost to external beam
radiotherapy with or without androgen deprivation therapy may be administered to improve
treatment outcomes [12].

Besides standard treatment options, there are a few minimally invasive therapies such as high-
intensity focused ultrasound (HIFU) and cryotherapy that can potentially be used for prostate
cancer as well. HIFU is a technique that uses focused ultrasound to generate areas of intense heat
to destroy tissue. Outside the focal zone, heat energy drops sharply, so the surrounding tissue
remains mostly unharmed. This technique is non-ionizing and can be safely repeated as it has no
long-term cumulative effects [9] [10]. Cryotherapy is a technique to ablate tissue by local induction of extremely cold temperatures. In this procedure, a thin metal needle is inserted into the prostate gland, which is then infused with freezing liquid such as liquid nitrogen or argon gas to destroy the cancerous tissue [11] [12].

1.2 Permanent Implant Prostate Brachytherapy

All risk group patients are eligible for permanent implant prostate brachytherapy. Patients with low-risk disease can be treated with brachytherapy as monotherapy. For intermediate-risk disease, brachytherapy may be combined with hormone therapy and sometimes external beam radiotherapy for effective treatment. For high-risk disease, a combination of hormone therapy with external beam radiotherapy and brachytherapy is suggested in the American Brachytherapy Society guidelines [17]. The following sections provide some technical and clinical background for LDR permanent brachytherapy.

1.2.1 Brachytherapy Sources

Radionuclides used for PIPB are $^{125}$I, $^{103}$Pd and $^{131}$Cs. For brachytherapy applications, the radioactive material is encapsulated in sealed, biocompatible capsules made of materials such as titanium and stainless steel. These capsules are most commonly cylindrical in shape, with nominal outer dimensions of 0.8 mm diameter and 4.5-5.0 mm length. They are often referred to as brachytherapy seeds.

Brachytherapy sources are available as loose (unconnected) seeds, or they can be linked together as connected strings, or “strands”. Seeds are implanted using multiple needles, with each needle
containing a train of seeds, usually separated by one or more non-radioactive spacers made from bio-absorbable suture material. In the case of strands, seed-spacer trains are enclosed by a tubular or braided membrane. Spacers have a smaller diameter than seeds and the most commonly used spacer length provides 1cm center-to-center seed spacing if the seeds are separated by a single spacer. Stranded seeds offer clinical advantages such as reduced seed migration and loss after implantation, and, consequently, reduced embolization to the lung [18]. They are therefore preferred by many clinicians.

Model AgX100 $^{125}$I stranded seeds (Theragenics, Buford, Georgia) are used at our institution for prostate brachytherapy. The AgX100 source consists of a cylindrical radio-opaque silver core, (3.50 mm length and 0.293 mm radius) coated with a 2 μm thick layer of radioactive AgI (silver iodide). The seeds are intentionally designed to contain a silver core to facilitate visualization on planar X-ray, fluoroscopy, or CT images. The silver core is encapsulated in a titanium tube. The overall source length is 4.50 mm and the active length is 3.50 mm [19]. A diagram of the AgX100 source is shown in Figure 1.2.

![Diagram of the AgX100 source model](image)

**Figure 1.2:** Schematic diagram of the $^{125}$I seed AgX100 source model
The two delivery methods for seed implantation are the preloaded needle and the afterloading techniques. In the first approach, the radiation oncologist (RO) inserts preloaded needles into the prostate tissue and seeds are deposited by retracting the needle against a stylet. Preloaded needles can be ordered in sterile assemblies from either the seed manufacturer, or through a third party. Alternatively, the needles can be loaded onsite, either prior to or during the procedure, by the hospital personnel; however, the loading process is time consuming and exposes the staff to extra radiation.

In the afterloading approach, the RO manually places empty needles in the patient and then an afterloading device, such as a Mick applicator or SeedSelectron [20], [21] is used to load the needles. The Mick applicator system allows loose seeds to be deposited one at a time, while the SeedSelectron builds the seed-spacer train and pushes it into the needle.

Afterloading or manual intraoperative preloading offer greater source placement flexibility compared to preoperative loading, and provide the potential for image-guided optimization of the implant by interactive planning in the operating room, which is described in more detail later in this thesis. However, this approach requires more time in the operating room. A hybrid alternative is to use a combination of previously loaded and intraoperatively loaded needles [22].

1.2.2 Brachytherapy Dose Calculation

The currently accepted methodology for clinical brachytherapy dose calculation is specified in the Task Group 43 (TG-43) report [23], [24] by the American Association of Physicists in Medicine. This formalism is based on calculation of dose rate to water at clinically relevant
distances (i.e. on the order of 1cm) around a brachytherapy seed. The total dose rate from all the
implanted seeds at a specific point is computed by summing the dose rate contribution from each
individual seed at that point. The TG-43 formalism accounts for effects of attenuation, scattering,
and absorption by the source encapsulation using a specific set of parameters, as outlined in
equation 1.7 and equation 1.8. However, heterogeneity in the medium or inter-seed attenuation is
not taken into account.

\[
\dot{D}(r, \theta, t) = \frac{\partial D(r, \theta, t)}{\partial t} = S_k(t) \Lambda \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} g_L(r) F(r, \theta) \tag{1.7}
\]

\[
\dot{D}(r, t) = \frac{\partial D(r, t)}{\partial t} = S_k(t) \Lambda \frac{G_p(r)}{G_p(r_0)} g_p(r) \varphi_{an}(r) \tag{1.8}
\]

Equation 1.7 shows the TG-43 two-dimensional (2D) formalism for the dose rate in water at
point \((r, \theta)\) with respect to the center of a seed. ‘\(r\)’ denotes the distance (in centimeters) from the
center of the brachytherapy seed to the point of interest and ‘\(r_0\)’ denotes the reference distance,
which is defined to be 1 cm in this protocol. ‘\(\theta\)’ denotes the polar angle of the point of interest
relative to the source longitudinal axis and ‘\(\theta_0\)’ is the reference angle, which is specified to be 90
degrees and defines the source transverse plane. The coordinate system used in the TG-43
dosimetry calculation is illustrated in Figure 1.3.
Equation 1.8 is the one-dimensional (1D) formalism for dose rate and is used when the orientation of the seed is undetermined. This equation depends only on distance from the seed and uses the solid-angle weighted average of the dose rate over all possible seed orientations.

For practical reasons, the source strength is specified in terms of air kerma. Air kerma is the total kinetic energy transferred to charged particles by photon interactions with atoms in air, per unit mass of air. The air kerma strength, $S_K$, is defined as the product of the air kerma rate at a given point in time for a source in vacuum, at distance $d$ from the source, and the square of this distance $d^2$. It is measured in units of $\mu\text{Gy.m}^2\cdot\text{h}^{-1}$ and is often denoted in the literature by the symbol ‘$U$’. The dose rate constant, $\Lambda$, gives the dose rate in water per unit air kerma strength at the reference point $(r_0, \theta_0)$, for a source surrounded by water. Values of $\Lambda$ are specific to the...
model (both type of radionuclide and physical source design) of brachytherapy source being considered. \( G(r, \theta) \) aims to account for dose variations due to divergence (inverse square law) effects, with some consideration of the spatial distribution of activity within the source. TG-43 specifies two models for the distribution of radioactivity, the point source model (\( G_P \)) and the line source model (\( G_L \)).

\[
G_P(r) = \frac{1}{r^2}
\]  
\[
G_L(r, \theta) = \frac{\beta}{L r \sin \theta} (\theta \neq 0) \quad \text{or} \quad \frac{1}{r^2 - \frac{1}{4} L^2} (\theta = 0)
\]

The radial dose function, \( g(r) \), accounts for the variation of dose rate with distance along the transverse axis of the source due to absorption and scatter by the medium (i.e. tissue or water), and is determined separately for the point source and line source models. The anisotropy function, \( F(r, \theta) \), accounts for the non-uniformities in dose rate due to source design and self-shielding by the seed encapsulation. However, for many applications, such as when source orientation is not known or not predictable, \( \theta \) is unknown and anisotropy is approximated by an anisotropy factor, \( \varphi_{an}(r) \), and the point source geometry is used.

The various TG-43 parameters and the exponential equation for radioactive source decay are combined to calculate the dose rate in water due to a single seed, at a given point in time relative to when \( S_K \) was determined (shown in the equations 1.11 for the full anisotropic version of the TG-43 equation):
\[
\dot{D}(r, \theta, t) = S_{k_0} e^{-\lambda t} A \left( \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \right) g_L(r) F(r, \theta) \tag{1.11}
\]

Where \( \lambda \) is the decay constant of the radionuclide (\( \lambda = \ln 2 / T_{1/2} \), where \( T_{1/2} \) is the half-life) and \( S_{k_0} \) is the initial value of the source strength (i.e. at the time of implantation). The total absorbed dose accumulated over time \( T \) is then computed as below:

\[
D(r, \theta, T) = \int_0^T \dot{D}(r, \theta, t) \, dt = \frac{S_{k_0}}{\lambda} \left( 1 - e^{-\lambda T} \right) A \left( \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \right) g_L(r) F(r, \theta) \tag{1.12}
\]

In the case of permanent implants, \( T = \infty \), which yields the following equation:

\[
D(r, \theta, T) = \frac{S_{k_0}}{\lambda} A \left( \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \right) g_L(r) F(r, \theta) \tag{1.13}
\]

For clinical purposes, dose calculation is performed using commercially available, Health Canada approved software, such as VariSeed (Varian Medical Systems, Palo Alto, CA).

1.2.3 PIPB Treatment Planning

All PIBP treatments are based on individualized treatment plans specifying the required \( S_K \) (where all seeds in the plan have the same \( S_K \)) and distribution of seeds within the target. The treatment planning procedure begins with identifying the target volume, usually on ultrasound. Patients undergo a TRUS imaging study of the prostate gland either a few weeks prior to or on the day of implantation, depending on the treatment planning approach used. The volume study consists of a series of axial images acquired with the patient in the dorsal lithotomy position.
using a TRUS probe. The prostate, and sometimes a small amount of neighboring tissue, is identified as the clinical target volume (CTV) on the ultrasound images. A margin to account for uncertainties in treatment delivery is then added to the CTV to create the planning target volume (PTV). Margin guidelines in our institution are 3 to 5 mm laterally, 0 to 3 mm anteriorly, 5 mm superiorly, and 0 mm posteriorly and 0-5 mm inferiorly.

The treatment plan identifies the arrangement of needles inside and sometimes around the PTV and also the position and strength of the seeds within each needle. A treatment plan for prostate brachytherapy implant is created with the goal of delivering the prescribed radiation dose (or greater) to the PTV, while minimizing dose to neighbouring organs at risk (OAR) such as the urethra, rectum and bladder, as much as possible. The recommended prescribed dose is 144 Gy for implants with $^{125}\text{I}$ sources [25] and 115 Gy for $^{103}\text{Pd}$ sources [26], if the patient is receiving brachytherapy as monotherapy. The prescription dose is defined as the minimum peripheral dose at the surface of the PTV. This is the dose that would be received by the PTV during an infinite period of time, but for example, essentially 99% of the dose is delivered in 12 months for $^{25}\text{I}$ with a half-life of 59.4 days.

The following criteria are recommended [27] when creating a treatment plan ($D_x$ represents the minimum dose received by $x$ cm$^3$ (cc) or $x$ percentage of the corresponding organ volume, where $D_x$ can be in units of Gy or percentage of the prescribed dose. $V_x$ represents the volume of the corresponding organ or target structure that receive $x$ Gy or $x$ percentage of the prescribed dose, where $V_x$ can be in units of cm$^3$ or percentage of the total volume):
CTV: $V_{100\%} > 95\%$, $D_{90\%} > 100\%$ and $V_{150\%} \leq 50\%$

Rectum: $D_{2cc} < 100\%$ and $D_{0.1cc} < 150\%$

Prostatic Urethra: $D_{10\%} < 150\%$ and $D_{30\%} < 130\%$

Beyond these criteria, there are several different approaches to the process of developing LDR brachytherapy treatment plans, as described below. The terminology proposed by the American Brachytherapy Society [28] for different approaches, is used in these descriptions.

1.2.3.1 Preplanning

TRUS volume study is performed a few weeks prior to the implantation. A treatment plan is created, which will be referred to as the preplan in this thesis. Usually, the seed and spacer configurations required by the plan are ordered from the vendor in the form of preloaded needles. On the day of implant, the prostate is implanted according to the preplan. An example of a needle loading report created from a preplan in our institution is shown in Figure 1.4. A number is assigned to each needle and the configuration of seeds and spacers within each needle is illustrated.
Figure 1.4: An example of the needle loading report created from a preplan. The second column in the table specifies the image plane in which the first seed of each needle is supposed to be deposited. The third column specifies the template grid location of the needle (see Figure 1.5 for an image of the grid itself).

<table>
<thead>
<tr>
<th>Needle Number</th>
<th>Retraction (cm)</th>
<th>Hole Location</th>
<th>Number Seeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>c4.5</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>d4.5</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>b4.0</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>0.00</td>
<td>C4.0</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0.00</td>
<td>E4.0</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>0.50</td>
<td>e4.0</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>0.00</td>
<td>B3.5</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>0.50</td>
<td>C3.5</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>0.50</td>
<td>E3.5</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>0.00</td>
<td>F3.5</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>0.50</td>
<td>a3.0</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>0.50</td>
<td>b3.0</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>0.50</td>
<td>e3.0</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>0.50</td>
<td>f3.0</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>0.00</td>
<td>B2.5</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>0.00</td>
<td>C2.5</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>0.00</td>
<td>E2.5</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>0.00</td>
<td>F2.5</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>0.50</td>
<td>a2.0</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>0.50</td>
<td>b2.0</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>0.00</td>
<td>c2.0</td>
<td>4</td>
</tr>
<tr>
<td>22</td>
<td>0.00</td>
<td>d2.0</td>
<td>4</td>
</tr>
<tr>
<td>23</td>
<td>0.50</td>
<td>e2.0</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
<td>f2.0</td>
<td>2</td>
</tr>
</tbody>
</table>

= Special loading
= Standard load
1.2.3.2 Intraoperative Preplanning

In this method, there is no need for a planning volume study before the implantation day, as the volume study is performed on the implant day in the operating room (OR). Immediately after image acquisition, the target volume is delineated on the images and a treatment plan is created. Seeds are then loaded into the needles in the operating room. In this scenario, the approximate number of seeds needed for implantation must be ordered beforehand, and is estimated from a nomogram or a table based on the prostate volume obtained from CT or ultrasound images taken previously for cancer diagnosis.

1.2.3.3 Interactive Planning

As in intraoperative planning, this method starts with a TRUS volume study performed in the OR on the same day as the implantation, and an initial treatment plan based on the acquired images. However, in interactive planning, the plan is modified frequently during the implantation based on live dosimetry feedback. Typically, a few needles are inserted according to the initial treatment plan, followed by assessment of the dose distribution based on estimates of the seed positions, obtained from, for example, visualization of the needle paths in TRUS images. Intraoperative MRI [29]–[32] is another option that has been explored for this purpose. If necessary, the needles may be repositioned before implanting the seeds, or subsequent needle positions may be altered in the treatment plan. If afterloading or intraoperative manual needle loading are options, the composition of the seed trains assigned to the needles can also be altered. This process is repeated depending on the radiation oncologist's preference.
1.2.3.4 Dynamic Dose Calculation

This method is similar to interactive planning except for the fact that treatment plan optimization is performed based on the actual deposited seed positions rather than seed positions estimated from the needle locations. Changes in prostate size and shape can be accounted for as well.

1.2.4 Implant Delivery

Prostate implantation is performed in the operating room, while the patient is in a dorsal lithotomy position and under general or spinal anesthesia. This procedure is usually guided by TRUS imaging, for which an ultrasound probe is inserted into the patient’s rectum to visualize the prostate gland. Air-filled gel is placed in the urethral catheter for visualization of the urethra. A gridded template and the ultrasound probe are attached to a mechanical stepper, which is held by a stabilizer unit mounted on the operating table. The template is set up against the perineum and a grid image corresponding to the template holes is electronically superimposed onto the ultrasound images to aid in positioning needles during implantation. An image of a brachytherapy stepper setup is shown in Figure 1.5. The ultrasound probes that are commonly used have both linear and curved ultrasonic crystals, which enable transverse and sagittal imaging. The RO uses the sagittal array of the ultrasound transducer for identification of needle insertion depth, as the needle track is usually easily visualized on these images. The curved array of the probe is used for axial visualization of the prostate. The probe can be easily translated craniocaudally with the stepper to scan the entire prostate. Approximately 50-150 seeds are deposited into the prostate tissue and some immediately surrounding tissue, according to a patient-specific treatment plan.
Figure 1.5: Brachytherapy stepper setup

Fluoroscopic imaging can be used in addition to ultrasound imaging for assessment of PIPB, as it provides good quality real-time images of the brachytherapy seeds. Intraoperative fluoroscopy is performed using a mobile C-arm fluoroscopic X-ray system, which can be rotated for anterior-posterior or oblique radiographic acquisition. C-arm machines are composed of an X-ray generator and an image intensifier or flat panel detector. Flat panel detectors are increasingly replacing image intensifiers, as they provide better image quality. C-arm cone-beam computed tomography (CBCT) with flat panel detector is a relatively new imaging technology that enables three-dimensional (3D) imaging in the OR.

1.2.5 Implant Dosimetry Evaluation

There are some technical and practical hurdles to implementing the treatment plan intraoperatively with precision. The primary source of uncertainty is difficulty in depositing
seeds as planned. The needles may deviate from the intended trajectory and, as a result, the seed train often follows a curved, rather than a straight, path after the needle is retracted. In addition, prostate movement occurs during implantation due to forces generated by the insertion or removal of needles, which creates additional uncertainties in implementing the treatment plan. Therefore, the quality of the implant has to be evaluated after the procedure is completed in order to determine if there is any need for additional treatment or if unwanted complications might occur. Additionally, it provides the physicians and medical physicists with a measure of the performance of the treatment plan and implant, allowing for continued technical improvement.

Implant evaluation involves calculation of the radiation dose received by the prostate and surrounding OAR. The following parameters are recommended to be reported in postimplant dosimetry evaluation [27], [33]:

Target volume (prostate or PTV):
- Primary parameters: D90%, V100% and V150%
- Secondary parameters: V200%, V150%, V90% and D100%

Rectum:
- Primary parameter: D 2cc
- Secondary parameter: D 0.1cc and V100%

Urethra:
- Primary parameter: D10%
- Secondary parameter: D 0.1cc, D30% and D5%
1.2.5.1 Evaluation Techniques

There are a variety of techniques and imaging modalities that can be used for implant evaluation. In order to perform dosimetric evaluation, the location of the implanted seeds relative to the prostate and OAR must be determined. The current standard of care to evaluate the implant is CT imaging [27]. Depending on local practice, the CT scan is typically acquired either a few hours or about four weeks after the patient has left the operating room. The prostate and OAR boundaries as well as seed locations are identified on the CT images and are used to calculate the dose received by these organs. However, CT images do not provide good soft tissue contrast and postimplant CT image quality is also degraded due to X-ray scattering by the seeds. MRI and ultrasound images have good soft tissue contrast and have shown less inter- and intra-observer variability in prostate contouring compared to CT images [34], but offer poor visualization of the seeds. CT-MRI fusion [35], [36] can be used for more accurate dosimetric evaluation, in centers where MRI is available. Examples of images acquired from a patient who received external beam radiotherapy first and then PIPB boost are shown in Figure 1.6. In this figure, preimplant MRI, preimplant CT (used for external beam treatment planning), preimplant TRUS and postimplant CT, are represented from left to right in the order they were taken. Bottom row images are the same as the corresponding ones in the top row with the prostate contour delineated on them. The contours were delineated manually by a radiation oncologist on each image, where any of the previously acquired images shown in the figure were available to the radiation oncologist for reference (including reference via image registration and fusion tools) if required. The prostate boundary is delineated in red in all images. As can be seen, the prostate boundary is visible on TRUS and MRI images, whereas it is not as easy to distinguish prostate from neighbouring tissue on the CT images, especially on the CT image acquired after the
brachytherapy implant. The white contour delineates a cancerous lesion that was visualized on the MRI images first and then identified on the TRUS image with the help of image fusion.

Dosimetric evaluation of the implant can be performed inside the OR, as well. Ultrasound imaging alone has been used for prostate boundary delineation and seed identification [37], [38]. In this method, TRUS imaging is used to visualize the needle tip and, potentially, also each individual seed as it is deposited. However, subsequent seed displacement after deposition is not taken into account and could have potential dosimetric consequences [39].

CBCT/Fluoroscopy is also routinely available in the OR, and is preferred for brachytherapy seed visualization as the seeds are designed for good visibility with X-ray imaging modalities. However, as already mentioned, these imaging modalities have low soft tissue contrast and, therefore, are not ideal for delineating the prostate and surrounding OAR. Ideally, then, the information obtained from intraoperative ultrasound imaging and CBCT/fluoroscopy should be combined for dosimetric evaluation in the OR. In other words, if the prostate boundary could be obtained from the ultrasound images and seed coordinates obtained either from a 3D reconstruction of fluoroscopic images [40], [41] or from 3D CBCT reconstructed images, registration of TRUS-fluoroscopy or TRUS-CBCT image sets could be used toward accurate intraoperative evaluation of the implant dosimetry [42]–[47]. This approach remains an area of development, and methods reported to date commonly use external fiducial markers [48] or optical trackers [49] to assist in image registration.
Figure 1.6: From left to right: preoperative MRI, preoperative CT, preoperative TRUS and postoperative CT images of a patient who received external beam radiotherapy and PIPB boost afterwards. The prostate boundary is delineated in red and the cancerous lesion is delineated in white. Contours in cyan, yellow-green and blue represent planning target volume, urethra and rectum, respectively. The contours were delineated manually on each image; however, reference (including use of image registration and fusion tools) to prior images was available during contouring.
1.2.5.2 Uncertainty in Dosimetry Evaluation

There are different sources of uncertainty [50] affecting postimplant dosimetry, depending on the evaluation technique used. One of the major sources of uncertainty is variability in prostate contouring. As mentioned before, use of CT images leads to larger inter- and intra-observer variability compared to TRUS and MRI modalities. One of the other factors contributing to dosimetry uncertainty is seed localization. It has been shown, for example, that a seed localization uncertainty of 2mm resulted in prostate D90% deviation of about 5% [51]. Seed localization uncertainty can be high, if seed locations are derived from needle location rather than actual deposited seed locations, as the shape of the seed train is often distorted after the needle is retracted. Seed trains may also be “dragged” inferiorly along the needle track as the needle is withdrawn from the tissue.

If dosimetry is evaluated by image registration from two or more imaging modalities, there are uncertainties depending on the timing and patient positioning for each scan. The optimal time for obtaining the postoperative scan is difficult to establish, so practice varies among different centers. Due to postimplant edema and its resolution, prostate volume and dosimetry change over time after the implant [52]. The edema effect decreases exponentially with time and it may take 2 to 25 days (mean 9.3 days) for the effect of edema to decrease by half [53]. However, in another study, 12% of prostates were found to have significant residual edema 1 month after implant [54].

Regardless of the dosimetric evaluation technique used, there are other sources of uncertainty that will affect the implant dosimetry. For dosimetric calculation, brachytherapy source strengths
are entered into the treatment planning system (TPS). However, there are uncertainties in both the source strength values and the dose calculation by the TPS. The sources that are shipped to the clinics for an implant do not all have exactly the same air kerma strength due to variabilities in the manufacturing process, and, for multiple reasons, it is not feasible to assign individually determined air kerma strengths to each seed in the final implanted distribution. Batch averages or nominal air kerma strengths are therefore typically used in the dose calculation. Combining these uncertainties with the estimated uncertainty in the TG-43 parameters used for dose calculation, the dose calculation uncertainty for low energy brachytherapy sources can be as high as 9% [55].

Furthermore, most treatment planning system dose calculations for prostate implants are based on the TG-43 1D formalism. Seed orientation, inter-seed attenuation and tissue composition effects are not taken into account. Monte Carlo simulation has shown that considering inter-seed attenuation and scattering in dose calculation leads to 5.8% to 12.8% differences in D90% as compared to the TG-43 formalism [56]. Ignoring the effects of seed orientation may cause up to 2% differences in the calculated dose [57], [58].

1.3 Thesis Overview

The main objective of this research project is to investigate the feasibility of performing real-time intraoperative dosimetry for permanent implant brachytherapy at our center, using a CBCT capable C-arm for accurate source localization and ultrasound imaging for prostate delineation. In this chapter, some clinical and physics background regarding prostate cancer and brachytherapy treatment was provided. An overview of the current literature of PIPB dosimetric evaluation techniques was also presented.
In chapter 2, the prostate brachytherapy procedure in our center is described. Also included in this chapter are the results of some preliminary work that was performed as part of this thesis to assess the uncertainties in implant delivery. These results helped to provide some of the context for the research motivation.

In chapter 3, the workflow for real-time intraoperative dosimetric evaluation of the prostate brachytherapy procedure is presented. The process of patient recruitment and steps of data collection in the operating room for the clinical study that was designed for the purpose of this research project are described. Two intraoperative dosimetry approaches are proposed. In both approaches, the implanted seed locations were obtained from X-ray imaging modalities (C-arm fluoroscopy or CBCT) and registered to the prostate boundary obtained from TRUS images. Registration was performed on the basis of a common subset of seeds identified on the two imaging studies. The effect of ultrasound probe pressure on the prostate shape was also taken into account by deforming the prostate boundary using a finite element model. The results from both approaches were compared with standard of care postimplant CT dosimetry.

In chapter 4, the automatic detection of seeds on ultrasound images is explored. This was motivated by the need to rapidly and accurately identify seeds on the ultrasound images as part of the proposed intraoperative workflow described in chapter 3. A convolutional neural network model was trained and tested on ultrasound images to localize the needle track first and then find seeds within the needle track. The results from the proposed method were compared to manual seed localization performed by an expert.
In chapter 5, the main results of this thesis are summarized and directions for future work in this research area are suggested.
Chapter 2: Prostate Brachytherapy at BC Cancer-Vancouver

2.1 Introduction

2.1.1 Overview of PIPB at BC Cancer-Vancouver

The BC Cancer PIPB Program was established in 1998 at BC Cancer-Vancouver. For prostate LDR brachytherapy, a modified version of the Seattle preplanning method [59] was and continues to be used. A few weeks before implantation, the patient undergoes a TRUS volume study, where a series of parallel axial images, spaced at 5mm, are collected from above the prostate base to below the apex. In current practice, a preliminary CTV is identified with the help of an in-house semi-automatic contouring software [60]. This CTV is then modified by the RO as required, and a PTV is created by adding margins to the CTV. A treatment plan is then generated manually by a Medical Physicist. Preloaded needles with $^{125}$I model AgX100 stranded seeds (Theragenics, Buford, Georgia) are used for implantation. On the implant day, TRUS and C-arm fluoroscopic imaging are used routinely by the RO to visualize the prostate gland and implanted seeds, respectively. A few hours after the implantation is completed, a CT scan is acquired, with a slice thickness of 2.5 mm, outside the operating room to evaluate the dosimetry of the implant. This will be referred to as Day 0 CT dosimetry. The prostate and OAR contours, along with seed locations, are identified on the CT images to calculate the dose received by each organ.

For postimplant quality assurance purposes, the implants are categorized into 3 groups, based on the calculated prostate D90% and V100%, as outlined in Table 2.1. There are no explicit thresholds currently recommended for urethra and rectum dose parameters, however, these
structures are planned to receive less than 150% and 100% of the minimum peripheral dose, respectively.

<table>
<thead>
<tr>
<th>Implant Quality</th>
<th>D90% Range</th>
<th>V100% Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>144Gy &lt; D90% &lt; 180Gy</td>
<td>V100% ≥ 90%</td>
</tr>
<tr>
<td>Good</td>
<td>130Gy &lt; D90% &lt; 144Gy</td>
<td>V100% ≥ 85%</td>
</tr>
<tr>
<td></td>
<td>or 180Gy &lt; D90% &lt; 200Gy</td>
<td></td>
</tr>
<tr>
<td>Sub-optimal</td>
<td>D90% outside the above ranges</td>
<td>V100% &lt; 85%</td>
</tr>
</tbody>
</table>

Based on the data from 1006 consecutive patients who received LDR-PIPB on or before October 2003, the 5-year and 10-year disease free survival rates, with a median follow-up of 7.5 years, were 96.7% (95% confidence interval [CI], 95.2%-97.7%) and 94.1% (95% CI, 92%-95.6%), respectively [61]. The actuarial rates of distant metastasis and disease-specific death at 5 years were both <1% [62]. These data show that PIPB achieves exceptional cure rates for low and intermediate risk cancers [63].

2.1.2 Limitations of Preoperatively Planned PIPB

Although excellent clinical outcomes have been achieved, there is still room for improvement [64], particularly in terms of the dosimetry. To illustrate this, a comparison was performed between pre- and postimplant dosimetric parameters of 1525 patients who have undergone PIBP, as a monotherapy, in BC Cancer-Vancouver between 2008 and 2019. Pre- and postimplant
dosimetric parameters were obtained from the preplan and postimplant Day 0 CT dosimetry, respectively. The prescribed radiation dose was 144Gy for all patients.

The kernel distribution fits of the histograms of D90\% and V100\% data are shown in Figure 2.1 and Figure 2.2, respectively. Tan regions in the graphs represent the suboptimal implants, based on the quality assurance measures presented in Table 2.1. Implants with suboptimal D90\% account for 2.75 \% of the data and implants with suboptimal V100\% account for 4.85 \% of the data. The urethra contours were only available on Day 0 CT images (urethra was not visible on TRUS images used for creating the preplan) and a kernel fit of postimplant urethral D30\% and D5\% is shown in Figure 2.3. Implants with D30\% and D5\% larger than 150\% of the prescribed dose account for 2.07\% and 16.53\% of the data, respectively.

Postimplant dosimetric coverage of the prostate, as measured by D90\% and/or V100\% of the prostate, is consistently lower and more widely distributed than in the preoperative treatment plan, as illustrated in Figure 2.1 and Figure 2.2. Any underdosed area in the suboptimal implants that contains prostate cancer foci may result in treatment failure. Conversely, implants with overdosed regions may cause unfavorable urethral or rectal toxicity. Intraoperative dosimetric evaluation at stages during the implant can improve the dosimetric outcome and result in less side effects [65], [66].
Figure 2.1: Kernel distribution function of the prostate D90% from preoperative treatment plan (preplan) and postoperative dosimetric analysis of 1525 patients treated with prostate brachytherapy at BC Cancer-Vancouver. D90% is represented as a percentage of the prescribed radiation dose. Tan regions of the graph represent suboptimal implant regions, as defined in our center.
Figure 2.2: Kernel distribution function of the prostate V100% from preoperative treatment plan (preplan) and postoperative dosimetric analysis of 1525 patients treated with prostate brachytherapy at BC Cancer-Vancouver. V100% is represented as a percentage of the contoured prostate volume. Tan regions of the graph represent suboptimal implants, as defined in our center.
Figure 2.3: Kernel distribution function of the urethra D30% and D5% from postoperative dosimetric analysis of 1525 patients treated with prostate brachytherapy at BC Cancer-Vancouver. Tan region of the graph represents implants with D30% and D5% receiving more than 150% of the prescribed radiation dose.

Factors contributing to the differences between preplanned and postoperative dosimetric parameters include:

a) Practical difficulties in accurately delivering the treatment plan on the implant day due to differences in patient position between the planning volume study (where the patient is awake) and the operating room (where the patient is anesthetized), or relaxation of the pelvic musculature due to anesthesia that may lead to changes in the prostate shape compared to the prostate contours obtained from the volume study TRUS images [67].
b) Technical challenges in accurately placing seeds within the soft tissue of and surrounding the prostate \[68\], in spite of using ultrasound and fluoroscopic imaging in the operating room for needle guidance and prostate visualization.

A few studies have investigated the displacement of seeds following the brachytherapy procedure \[69\]–\[71\], and identified displacement of \(^{125}\)I sources from their intended locations; however, very small data sets were used in all of these studies. In this chapter, a detailed regional analysis of implanted versus planned source locations was carried out on a large data set of 178 patients, in order to better understand the type and magnitude of source placement errors that might lead to suboptimal dosimetry.

### 2.2 Materials and Methods

Data were obtained from a cohort of 178 patients that were selected randomly from our BC Cancer prostate brachytherapy database. In order to study source placement error, three parameters, including implanted depth error, deviation and splay, were investigated, by comparing the postoperative seed cloud, obtained from Day 0 CT images, to the preplanned seed locations. As part of the routine postimplant dosimetry analysis for all patients at our center, an in-house software \[72\] is used to localize implanted seeds in Day 0 CT images. This software finds the seeds corresponding to each strand and labels the strands according to the assigned needle number in the treatment plan. This information was used as the starting point for comparing the planned and implanted seed clouds, as follows.
First, the planned and implanted seed clouds were translated to a common coordinate system where the origin was assigned to the common center of mass of the seed clouds. Then seed locations obtained from Day 0 CT images were rotated relative to the preplan seed locations in order to account for the difference in patient position (supine versus lithotomy) between the CT and TRUS image acquisitions. To do so, source locations within each seed train identified on a given Day 0 CT scan were fitted with a line in 3D space, and the angle of this line relative to the coronal plane of the CT image set was determined. The median value of all the angles was then used to rotationally align the implanted seed cloud with the preoperative seed cloud of the treatment plan (in which all needle paths run parallel to the ultrasound probe), thus compensating for the difference in patient position during ultrasound versus CT.

In order to calculate the implanted depth error, two or four intraprostatic lateral needles, with the same retraction plane, were chosen from the preoperative plan for each patient. The corresponding seed trains were identified in the implanted seed clouds as well. The chosen lateral needles were used to define a superior-inferior reference plane in both preplan and implanted seed cloud, the underlying assumption, based on physician feedback, being that these lateral needles were amongst the easiest to implant and were therefore the most likely to have been placed relatively accurately. The reference planes of the preplan and implanted seed clouds were then aligned in the superior-inferior direction for comparison of seed train insertion depths between the two clouds. The difference between the superior positions of the preplanned and implanted seed trains were calculated and this is referred to as the implanted depth error. A schematic diagram of the planned and implanted positions of selected strands from one of the cases is illustrated in Figure 2.4.
Figure 2.4: An example of the planned and implanted positions of selected strands from one of the cases. Seed trains from the preplan are shown in blue and the implanted seed trains are shown in pink. The reference plane is defined by the location of the lateral seed trains, number 5 and 6, from the preplan. Definition of the implanted depth error is shown for strand #9.

In addition, needle deviation and splay, as represented by the implanted seed train coordinates in the transverse plane, were calculated. Deviation refers to the average perpendicular distance of seeds within a train from the fitted line; and splay is the angle that the fitted line makes with the mid-sagittal plane, where lateral splay was assigned a positive value and medial splay a negative value. Examples of needle deviation and splay are illustrated in Figure 2.5 and Figure 2.6, respectively.
Figure 2.5: Representation of implanted seed train deviation from a straight line that is fitted to the location of the seeds in the train.

Figure 2.6: Representation of implanted seed train splay in the coronal view.
The midplane of the preplan seed cloud was found in the anterior-posterior direction and, based on that, seed trains were assigned to two regions, anterior and posterior.

2.3 Results

In total, the source placement errors of 2196 seed trains in the anterior region and 2631 seed trains in the posterior region of the prostate were evaluated from a cohort of 178 patients. Histograms of implanted depth error, deviation and splay are illustrated in Figure 2.7, Figure 2.8 and Figure 2.9, respectively. The median values of calculated implanted depth error, deviation and splay are reported in Table 2.2 for anterior and posterior regions of the prostate. Negative implanted depth error indicates inferior displacement with respect to the reference plane while positive values indicate superior displacement. Figure 2.7 shows that the histogram of implanted depth error in the anterior region is shifted more toward the negative values while it is more shifted toward the positive value in the posterior region of the prostate; with a larger median value of net error in anterior region. Needle deviation was relatively small in both the anterior and posterior prostate. Splay was mostly lateral and somewhat larger in the anterior region as compared to the posterior region.
Figure 2.7: Histogram of implanted depth error for anterior and posterior regions of the prostate obtained from a cohort of 178 patients. Negative implanted depth error indicates inferior displacement with respect to the reference plane while positive values indicate superior displacement.
Figure 2.8: Histogram of implanted seed train deviation for anterior and posterior regions of the prostate obtained from a cohort of 178 patients.
Figure 2.9: Histogram of implanted seed train splay for anterior and posterior regions of the prostate obtained from a cohort of 178 patients.

Table 2.2: Analysis of source placement error for prostate brachytherapy permanent implant from a cohort of 178 patients, in terms of implanted depth error, deviation and splay

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanted depth error (mm)</td>
<td>median</td>
<td>-1.9</td>
</tr>
<tr>
<td>Deviation (mm)</td>
<td>median</td>
<td>0.5</td>
</tr>
<tr>
<td>Splay (degree)</td>
<td>median</td>
<td>5.3</td>
</tr>
</tbody>
</table>
2.4 Discussion and Conclusions

The results from this study suggest that the anterior prostate is more prone to implanted depth errors, deviation and strand splay and are consistent with results reported in previous studies that used a different methodology and smaller sample sizes [69], [71]. The seeds are placed more inferiorly in the anterior part of the prostate which is possibly due to a lack of tissue in the region close to the bladder, making it more difficult to place seeds there. These results are consistent with the findings of other studies that investigated the dosimetric impact of source misplacement rather than quantifying the source placement error. The results from these studies showed that the prostate base receives lower dose than what it is planned to receive [73] and that the anterior-superior quadrant of the prostate, on average, receives significantly lower dose compared to the other quadrants of the prostate [74],[75].

One limitation of this study is the assumption that the needles used to define the superior-inferior reference plane were implanted to the intended insertion depth. Although this assumption was made based on feedback from physicians, it may not be true for all patients. Additionally, the rigid registration applied to the implanted seed cloud to align it with the preplan seed cloud is subject to some uncertainty as it did not account for the effects of tissue deformation due to the change in patient position and presence/absence of the ultrasound probe in the two image sets. The results of this study estimated the differences between preplanned and implanted seed locations. These differences can be the result of physical seed misplacement or tissue deformation caused by the abovementioned factors as well as edema or needle insertion forces, which are unavoidable in the process of implantation.
Dosimetric analysis of the PIPB procedures performed in our center, as illustrated in Figure 2.1 and Figure 2.2, showed that while the implants were planned to receive D90% between 105% and 133%, most of the implants actually received less dose than planned. The result from the V100% distribution also shows that implants didn't achieve the dose coverage that was planned.

Other than source placement error, factors that may contribute to this difference include the fact that the prostate-CTV was contoured on ultrasound images for the preoperative treatment plan, but it was contoured on Day 0 CT images for postimplant dosimetry. It has been reported that the prostate volume derived from the CT images is generally larger than that of the TRUS by a factor of 1.5 [76] or 1.3 [34], even though it includes no CTV expansion. The ratio of preimplant prostate volume (obtained from TRUS images) to postimplant prostate volume (obtained from Day 0 CT images) was calculated for each patient in the cohort of 1525 patients and its histogram is illustrated in Figure 2.10. The median value of this ratio was 1.2 in our study group.

Delineating a distinct boundary for the prostate on CT images is not trivial as it is not well resolved from other adjacent soft tissue structures, as discussed previously in the Introduction. Difficulty in differentiating the posterior surface of the prostate from the anterior wall of the rectum, the apical portion of the prostate from the anterior portion of the levator ani muscles and the prostate boundary from the neurovascular bundles have been described as the most significant challenges in defining the prostate volume on CT images [77].
Another contributing factor is the dosimetric impact of edema. It has been shown that prostate volume after implantation can increase by 52% on average [53]. In our center, postimplant dosimetric analysis was performed on the day of the implant, where edema is at its maximum, therefore, the delivered dose may be underestimated [78]. Factors such as initial size of the prostate, anisotropy in edema and margins of PTV vary for each patient and can affect the dosimetric parameters differently in each patient. Day 0 CT dosimetry has the advantage of patient convenience as dosimetry is evaluated after the patient has left the operating room and no further visit to the clinic is required; however, if the evaluation is not adequate, corrections to the implant have to be done on a different day.
All of the abovementioned factors may cause dosimetric deviations from the treatment plan. Each of the imaging modalities currently used in the OR has limitations in providing the required information for prostate brachytherapy dosimetry. Therefore, only qualitative assessment of the implant is performed in the operating room. Currently, a few extra seeds and needles are ordered for each patient to be implanted if deemed necessary. However, any modification of the original plan in the operating room is operator dependent and subject to being suboptimal as there is no immediate feedback on its overall dosimetric impact. Therefore, quantitative evaluation of the implant in the OR is desirable and can improve the implant dosimetry.
Chapter 3: Intraoperative Dosimetric Evaluation of PIPB

3.1 Introduction

3.1.1 Motivation

In current practice, TRUS and fluoroscopic images are used routinely in the operating room to visually evaluate implant quality but do not provide quantitative data for dosimetry purposes. Seeds are easily visualized in fluoroscopic images, but are difficult to locate in ultrasound images, particularly once many seeds have been implanted. On the other hand, the prostate boundary is more visible on the TRUS images and cannot be seen in fluoroscopy images.

As demonstrated in chapter 2, implanted source positions do not always exactly match the preplan due to several factors such as needle deviation, tissue deformation, and prostatic edema. Thus, dosimetric evaluation at stages during the implant procedure is desirable. Intraoperative dosimetric evaluation will provide the physician with the opportunity to perform quantitative assessment of the implant while the patient is still on the operating table and apply adjustments to the treatment plan. With this goal in mind, this thesis project was defined with the purpose of improving the PIPB procedure by developing an intraoperative dosimetric evaluation method that can provide rapid dosimetry feedback, and potentially also eliminate the need for postimplant Day 0 CT dosimetry.

The workflow envisioned for implementation of intraoperative dosimetry is as follows: The prostate boundary is obtained from the TRUS images and the 3D location of the seeds is obtained from either fluoroscopic images or CBCT images (depending on the stage of the
implantation procedure), and then the registration of the two image sets is used toward quantitative evaluation of the implant inside the OR while the patient is still on the bed, rather than having to wait for CT-based evaluation hours after completion of the implant.

3.1.2 Previous Works

Several groups have worked on combining TRUS and X-ray imaging modalities (CBCT or fluoroscopy) for dosimetric evaluation of the prostate brachytherapy implant, and have shown that this method has potential for adaptive dynamic dose calculation that will enable steps to be taken to improve prostate dose coverage [79]–[86]. However, there are still some limitations to this approach. For example, currently registration of these two imaging modalities is usually performed using external or internal fiducial markers. However, fiducials are unwelcome additions to the permanent brachytherapy procedure, and the X-ray projection of the fiducial markers can overlap the implanted seeds [48] and hamper automatic seed segmentation. Also, setting up the C-arm in a position where the fiducial markers and all implanted seeds are in the same field of view but do not overlap can be very challenging considering the limited space between the knees of the patient in lithotomy position.

Furthermore, changes in the prostate shape and position between the TRUS and X-ray imaging modalities are usually not taken into account. X-ray imaging is more reliable when the ultrasound probe, which can diminish seed contrast, is retracted. It is also common for the radiation oncologist to apply upward pressure on the probe when acquiring ultrasound images. The magnitude of applied force is user dependent and results in a deformation of the prostate. A geometric model to simulate this deformation has been investigated [60], [87] and one study of
the potential dosimetric impact of this deformation [88] has demonstrated a small but non-negligible effect.

In this chapter, a study investigating the feasibility of performing intraoperative dosimetry with TRUS-fluoroscopic and TRUS-CBCT registration is described. Instead of using fiducial markers, a common set of seeds identified on TRUS and fluoroscopy or CBCT image sets was used for image registration. This concept has been investigated previously as a means of registering intraoperative TRUS-based contours to Day 0 postimplant CT [89], and is possible because the initial TRUS image set is captured after implantation of seed trains from only a few needles, when tissue trauma and artifacts are low and individual seeds are still reasonably easy to identify. The effect of probe pressure on the prostate shape was also explored by deforming the prostate contours using a finite element model (FEM). In this algorithm, implanted seeds were used as control points and their movements were used to characterize the prostate deformation.

3.2 Materials and Methods

3.2.1 Data Collection

A clinical study was designed and the approval of the Research Ethics Board of the University of British Columbia was obtained. Patients who were eligible for receiving LDR PIPB were considered for this study. Supplementary imaging interventions were acquired from the patients during the implantation in addition to their standard brachytherapy procedure. Images were then processed outside the operating room to investigate feasibility of the proposed intraoperative dosimetry methods, with the ultimate goal of implementing these methods inside the operating room. The primary objective of this clinical study was to investigate the feasibility of performing
The secondary objective was studying the deformation of the prostate tissue and changes in the implanted seed distribution after the probe removal. The following sections provide an overview of the patient recruitment procedure and imaging interventions performed.

### 3.2.1.1 Patient Recruitment

All men who were eligible to receive LDR-PIPBA at our institution were also eligible for participating in this research study. Only patients who had some prior history of cancer (except some types of skin cancer) and had previous radiotherapy to the pelvis could not participate in this study. The clinical characteristics of all the study patients are shown in Table 3.1.

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical T-classification</th>
<th>Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Range</td>
<td>T1</td>
</tr>
<tr>
<td>63</td>
<td>47-75</td>
<td>38%</td>
</tr>
</tbody>
</table>

In the volume study session, i.e. a few weeks before the implantation, radiation oncologists discussed the research study with the eligible patient and provided him with the consent form. A follow-up phone call was made with the patient regarding his participation in the study. On the implant day, before entering the operating room, the consent form was signed by the patient in the presence of the radiation oncologist. 5 - 30 minutes extra OR time was booked for the
implantation procedure of the consented patients, depending on the study group they were assigned to. Patients were assigned to three different groups (details in section 3.2.1.3 below) in a chronological order of the implantation date, until the required number of patients was recruited for each group.

3.2.1.2 Imaging Interventions

Imaging interventions acquired for this study are listed below. Consented patients received a few of these imaging interventions, depending on the group they were assigned to. The imaging interventions will be referred to by their number in the list below, hereinafter.

1. A sagittal cine loop C-arm scan of the prostate.
   
   A cine loop consists of several fluoroscopic images that are acquired in sequence and can be displayed like a movie. This scan was acquired at the end of implantation, while the TRUS probe was being retracted through the length of the prostate.
   
   This scan was obtained with the purpose of studying the dynamics of the implanted seed distribution as a representation of the prostate movement and deformation.

   
   A TRUS volume study was done in the form of a series of 2D transversal B-mode images, with a standard increment of 5 mm, from above the base to below the apex, using the transverse transducer array of the probe, by retracting the probe manually.
These images were taken partway through the implant to allow seeds to be identified relatively easily on TRUS images and to prevent the prostate boundary visibility from being unduly affected by the scattering effect from the implanted seeds.

Prostate contours were delineated on TRUS images and the locations of the implanted seeds were manually identified on these images.

3. A sagittal TRUS volume study of the prostate gland.

TRUS radio frequency (RF) data were collected, using the sagittal transducer array of the probe, by automatic rotation of the probe around its longitudinal axis.

These images were taken partway through the implant.

3D TRUS B-mode images were created from the radio frequency data. Prostate contours were delineated on these images and the locations of implanted seeds were manually identified on these images. Additionally, TRUS RF signals were used to investigate the automatic detection of implanted seeds in the TRUS images. (described in chapter 4)

4. Three to five 2D fluoroscopic images at 0, ±5 and ±10 degree angles around the patient's mid-sagittal plane. These images were taken partway through the procedure, i.e. after a few needles had been implanted and the TRUS probe was still inside the patient’s rectum (probe-in).

These 2D fluoroscopic images were acquired immediately after the TRUS image acquisition. The locations of the implanted seeds were obtained from the 3D reconstruction of the fluoroscopic images to assist in seed identification on TRUS images. Initially five fluoroscopic images and later three images were taken. This change
was made in order to reduce the number of extra imaging interventions that patients
would receive, with consideration of the fact that three multi-view fluoroscopic images at
this stage, when the number of implanted seeds is low, would suffice for identifying the
3D location of the implanted seeds.

5. Five 2D fluoroscopic images at 0, ±5 and ±10 degree angles around the patient's
midsagittal plane. These images were taken at the end of the procedure, after all the seeds
had been implanted and while the TRUS probe was still inside the patient’s rectum
(probe-in). These images were taken to obtain the implanted seed locations from 3D
reconstruction of fluoroscopic images, while the probe was in.

6. Five 2D fluoroscopic images at 0, ±5 and ±10 degree angles around the patient's
midsagittal plane. These images were taken at the end of the procedure, after all the seeds
had been implanted and the TRUS probe was retracted (probe-out). During this image
acquisition, the patient was still in lithotomy position.
These images were taken to obtain the implanted seed locations from 3D reconstruction
of the fluoroscopic images, while the probe was out.

7. A 3D CBCT scan of the pelvic area.
This scan was acquired at the end of implantation with the patient in a supine position.
Isocentric fluoroscopic images were captured in an uninterrupted 135 degree motor-
driven rotation of the C-arm. Prior to the 3D scan, the scan center of the C-arm was
calibrated to be near the prostate center with the help of anterior-posterior and lateral
images; and a collision check was performed to assure that the C-arm did not collide with any obstacle while rotating around the patient. This process took approximately 3-4 minutes.

The multiplanar reconstruction of the images was performed by proprietary Ziehm (see below) software using a filtered back projection algorithm, which generates a 256×256×256 voxel 3D image set with a resolution of 0.5mm/pixel in all three directions. Examples of an axial and a sagittal slice from the reconstructed images is shown in Figure 3.1. The locations of the implanted seeds were obtained from these images.

Figure 3.1: Axial (left) and sagittal (right) slice views of a CBCT reconstructed image taken at the end of the prostate brachytherapy implant.

The cine loop scan, fluoroscopic images and 3D CBCT scan were acquired with a Ziehm Vision FD Vario 3D machine (Ziehm Imaging GmbH, Nürnberg, Germany), shown in Figure 3.2. This machine is a mobile C-arm with a flat-panel detector.
A BK Medical Flex Focus ultrasound machine (BK MEDICAL, Denmark) was used for axial TRUS volume studies of the prostate. A custom made 3D ultrasound data acquisition apparatus, along with a BK Medical Pro Focus ultrasound machine (BK MEDICAL, Denmark) with a research interface, were used for sagittal TRUS imaging. In this system, an EXII stepper (CIVCO Medical Solutions, Kalona, IA) was modified by motorizing the cradle rotation, allowing for automatic rotation of a dual-plane endorectal probe around its longitudinal axis, controlled by a personal computer. The sagittal transducer array within the probe was used for collection of TRUS RF ultrasound signals. The transrectal ultrasound probe rotation was from −45 to 45 degrees, where 0 corresponds to the probe aligned with the patient’s mid-sagittal plane. 450 frames were collected in one rotation (one frame at each 0.2 degree) and their corresponding angles were recorded. Each frame was 5.5 × 6 cm² (in superior-inferior and anterior-posterior directions, respectively). The TRUS RF data were then processed and 3D B-mode images, with a resolution of 0.25 mm/pixel in all three directions, were created.
3.2.1.3 Patient Cohort

Three groups of patients were considered in this study and each group underwent a few of the imaging interventions described above. Imaging interventions in each group were selected based on the objectives of this clinical study and also with consideration of the extra radiation dose received by a patient in each group. Extra radiation doses that patients received in this study are low compared to image guided external beam techniques that use daily kilo voltage planar or CBCT imaging for patient positioning and target localization. Wen et al. showed that CBCT imaging dose delivered to a pelvic site can range from 3 cGy/fraction to the central tissue to 4.8 cGy/fraction to most of the peripheral tissues and more than 9.5 cGy to the left hip joint region, where there is a 10° over scan of the CBCT source [90]. This can sum up to a high cumulative dose considering that these patients are typically treated for 36-38 fractions. However, the reported dose from a pelvic CBCT scan using mobile C-arm machine is at most 37 mGy [91], [92]. Also, a typical fluoroscopic entrance exposure rate is approximately 20 mGy/min [93]. The duration of the supplementary fluoroscopic images or cine loop scan taken in this study was in the order of a few seconds.

Group 1 (8 patients):

- A sagittal cine loop C-arm scan of the prostate (imaging intervention 1).

Group 2 (7 patients):

- Three to five 2D fluoroscopic images at 0, ±5 and ±10 degree angles around the patient's midsagittal plane, repeated three times (imaging interventions 4, 5 and 6).
- An axial TRUS volume study of the prostate gland (imaging intervention 2).
• A 3D CBCT scan of the pelvic area (imaging intervention 7).

Group 3 (8 patients):
• Three to five 2D fluoroscopic images at 0, ±5 and ±10 degrees angles around the patient's mid-sagittal plane, repeated three times (imaging interventions 4, 5 and 6).
• A sagittal TRUS volume study of the prostate gland (imaging intervention 3).
• A 3D CBCT scan of the pelvic area (imaging intervention 7).

For fluoroscopic imaging in Group 2, a digital level was attached to the top of the C-arm flat panel detector, and the unit was rotated manually to the desired angle. However, at the time of data collection for Group 3, fluoroscopic imaging was simplified by a precise C-arm angle encoder provided by the C-arm manufacturer. Fluoroscopic imaging angles varied slightly between individual patients; angle read-outs were obtained at a minimum resolution of 0.01 degrees.

In this chapter, the intraoperative dosimetry of PIPB has been evaluated using data from seven patients of Group 2 and six patients of Group 3. Two patients of Group 3 were not included in the analysis as the C-arm machine malfunctioned during CBCT imaging and their data set was incomplete. Results from analysis of Group 1 patients’ data are also discussed in this chapter.

3.2.2 Seed Segmentation

For 3D seed localization from 2D fluoroscopy images, the back projection method described by Dehghan et al. [94] was implemented and used. In summary, this method estimates the C-arm
pose from the recorded rotation angles while employing a computational method to compensate for C-arm sagging. The 3D seed locations are then identified by minimizing the distance between back projected lines from seed shadows in the fluoroscopic images. This method showed a localization (reconstruction) error of $0.86 \pm 0.44 \text{ mm}$ in a phantom study [94] with C-arm rotational pose errors of less than 1 degree. The reconstructed 3D coordinates of all the implanted seeds were obtained from five fluoroscopy views, with the TRUS probe both inserted (imaging intervention 5) and retracted (imaging intervention 6). These data sets will be referred to as the “probe-in seed cloud” and “probe-out seed cloud”, respectively.

Implanted seed locations on reconstructed CBCT images were determined using a combination of threshold filtering and visual inspection. The 3D coordinates of the seeds identified on these images will be referred to as the “CBCT seed cloud”.

Seed localization on the ultrasound B-mode images was performed manually, with the help of the mid-implant fluoroscopic image set reconstruction. No distinction will be made between patients in Groups 2 and 3 when comparing computed doses.

3.2.3 Prostate and Urethra Segmentation

The prostate boundary was delineated by an experienced RO on TRUS B-mode images. Since only a few seed strands were implanted at the time of ultrasound image acquisition, prostate boundary visibility was not affected by ultrasound scattering from the seeds or strand material. Due to the presence of contrast material in the catheter at the time of the 3D CBCT scan, the
location of the urethra could be estimated on the reconstructed CBCT images. The urethra was represented by a curved cylindrical volume with a radius of 0.5 cm, centered on the catheter.

### 3.2.4 Registration of TRUS and Fluoroscopy/CBCT Images

The seeds from the strands implanted at the time of TRUS imaging were identified within the CBCT or fluoroscopic postimplant seed cloud, with the help of the plan reconstruction software [72], described previously in section 2.2. A sample output from the plan reconstruction is illustrated in Figure 3.3. This figure also illustrates the problem of overlapping seeds in a single 2D view of the implant. This requires multiple views to be displayed and analyzed during the process of seed identification and plan reconstruction. Registration of the prostate contour from TRUS images to the full implant seed locations, obtained from fluoroscopic image reconstruction or CBCT images, was facilitated through the rigid registration of the common seeds between TRUS and CBCT or fluoroscopic images using the iterative closest point (ICP) algorithm [95], which minimizes the difference between the two sets of points.
Figure 3.3: A coronal view of the seed cloud from a reconstructed brachytherapy implant. Strands are identified by lines connecting the seeds. Each strand is labeled with the number used to identify it in the treatment plan. The strands that had been implanted at the time of TRUS imaging for this study patient [needle numbers 4, 5, 9 and 12] are shown in red, while the remaining strands are shown in green.

3.2.5 Prostate Deformation Using Finite Element Model

In order to account for the differences in prostate shape and position between TRUS imaging and fluoroscopy/CBCT imaging, a deformation model was applied to the prostate contours, using seed displacements as control points, to acquire the prostate boundary in the absence of the TRUS probe. The deformation model employed was a linear stress-strain finite element model described in Goksel et al. [96], [97]. First, the prostate was segmented on the TRUS B-mode
images, which will be referred to as the “TRUS prostate contour”. A binary mask of the contours was created and converted into a triangular surface mesh representation. A tetrahedral mesh model was then constructed for the entire ultrasound image volume including the prostate. The algorithm considered the ultrasound volume to be a box with its eight corners as fixed boundary constraints. A Young’s modulus and Poisson’s ratio pair of (50 kPa, 0.49) was used for the prostate and (15 kPa, 0.45) for the surrounding tissue, based on Nir et al. [98].

In the description of the FEM algorithm, the probe-in seed cloud is referred to as the “source” seed cloud and either of the probe-out or CBCT seed clouds is referred to as the “target” seed cloud. The plan reconstruction software [72] was used to identify the seeds associated with each strand and label them in the source and target clouds. Using the correspondence of seeds in the source and target clouds, the target seed cloud was rigidly registered to the source seed cloud to compensate for gross motions of the prostate, i.e. translation and rotation. The location of each seed in the source cloud was then compared to its corresponding seed in the target cloud and the residual displacement of each seed was calculated. This residual displacement was provided as input to the FEM algorithm to find the node displacements. The decompressed prostate contours were obtained from the resulting deformed mesh and will be referred to as the “probe-out” prostate contour or “probe-out supine” prostate contour, depending on whether the probe-out seed cloud, obtained from 3D reconstruction of fluoroscopic images, or the CBCT seed cloud was used as the target. A schematic diagram of the FEM is illustrated in Figure 3.4.
Figure 3.4: A schematic diagram of the finite element model (FEM): The prostate boundary was delineated on TRUS images, and a binary mask of the prostate was created and converted into a triangular surface mesh representation. A tetrahedral mesh model was then constructed for the entire ultrasound volume including the prostate. The seed displacements from probe-in to probe-out seed cloud were given as an input to the FEM to infer the prostate boundary in the absence of the probe.

3.2.6 Dosimetric Assessment

Two intraoperative dosimetric approaches were compared in this study: “CBCT-dosimetry” and “Fluoro-dosimetry”. The overall workflow leading to data acquisition for these two approaches is presented in Figure 3.5.
In both the CBCT-dosimetry and Fluoro-dosimetry approaches, prostate contours were obtained from TRUS images taken partway through the implant, and the locations of all the implanted seeds were obtained either from the CBCT or the probe-out fluoroscopic images. The seed coordinate locations and prostate contours for both CBCT- and Fluoro- dosimetry were exported to VariSeed 9.0 (Varian, Palo Alto, California) software for dosimetric evaluation. The results were compared to the standard of care Day 0 CT dosimetry.

For more detailed analysis of the spatial distribution of dose, sector analysis of the prostate was performed for both intraoperative dosimetric approaches using the tools available in the VariSeed software. Twelve sectors were generated by dividing the prostate longitudinally into

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*FEM = finite element model, †TRUS = transrectal ultrasound, ‡CBCT = cone beam CT

**Figure 3.5: The outline of proposed intraoperative dosimetric evaluation approaches.**
base, mid-gland, and apex sections, and then dividing each of these into four axial quadrants each. A schematic diagram of the prostate sectors is shown in Figure 3.6.

![Figure 3.6: Schematic diagram of 12 prostate sectors used in dosimetric analysis.](image)

3.2.7 Uncertainty Analysis

Analysis was performed to estimate the dosimetric uncertainty for each method. The main sources of uncertainty were seed localization and prostate contouring. For the intraoperative dosimetry methods, the average post-registration distance between the subset (of all implanted seeds) of seeds present in both the ultrasound and fluoroscopic/CBCT image sets was used as an estimator of the overall seed localization uncertainty. This seed localization uncertainty was assumed to incorporate the effect of prostate edema progression between the mid-implant and postimplant image acquisitions. The dosimetric effect of the seed localization uncertainty was estimated in a simulation that shifted the seed cloud by the absolute value of the computed localization uncertainty in anterior, posterior, superior, inferior, right and left directions, and then calculated the dosimetric parameters for each of these shifts. The resulting standard deviation of each dosimetric parameter was reported as the uncertainty in that parameter due to seed localization uncertainties.
In order to determine the dosimetric effect of prostate contouring uncertainty, a study to measure interobserver variability in prostate contouring on ultrasound and CT images was conducted. The prostate boundary was delineated by three experienced radiation oncologists on ultrasound images (acquired partway through the implant) and standard of care Day 0 CT images of all the study patients. The dosimetric parameters were calculated for each contour, and the standard deviation of each dosimetric parameter, averaged over all patients, was reported as the contouring uncertainty associated with that parameter. Uncertainties in each of the prostate dosimetric parameters due to seed localization and contouring were added in quadrature to calculate the total uncertainty associated with that parameter.

3.3 Results

3.3.1 Prostate Deformation

Rigid registration of the probe-out seed cloud to the probe-in seed cloud showed that the main translation of the prostate organ is in the cranio-caudal (Z-axis) and anterior-posterior directions (Y-axis), and its main rotation is around the patient’s right-left (X-) axis (sagittal tilt), all of which are expected, due to the probe pressure. After probe removal, the average seed cloud rotation about the X-axis was 5.4 degrees (with the base moving posterior) and the average translations were found to be 2.4 mm posteriorly and 3.3 mm superiorly. Translation and rotation in other directions were very small. After rigid registration, not all seeds in the probe-out seed cloud matched their corresponding location in the probe-in seed cloud, as expected, due to the deformation caused by the probe. The residual differences between corresponding seed locations were computed and the average root mean square difference (RMSD) was calculated to be 0.58 mm in the X-direction, 1.08 mm in the Y-direction and 0.57 mm in the Z-direction. An example
of the residual seed displacement after probe removal for one of the study patients is shown in Figure 3.7. The same calculation was performed for residual differences between probe-in and CBCT seed clouds. The calculated values were 1.20 mm in the X-direction, 1.25 mm in the Y-direction and 1.91 mm in the Z-direction.

Figure 3.7: An axial view of the brachytherapy seed displacement due to prostate deformation after transrectal ultrasound probe removal, overlaid on the registered prostate contour (the scale used for display of arrows is different from the scale of prostate contour.)

The average post-registration residual displacements over all patients were calculated for different regions of the prostate, which is also illustrated in Figure 3.8. Seeds in the posterior region of the prostate drop downward and the seeds in the lateral regions move medially and anteriorly. The seeds in the apex moved downward after probe removal, whereas they moved
toward the mid-gland and downward when the patient was put into the supine position. Similar
effects were seen at the posterior base.

Figure 3.9 shows an axial view of a patient’s prostate TRUS B-mode image. The figure
illustrates the TRUS prostate contour in blue and the FEM inferred contours in red (probe-out
contour in lithotomy position) and yellow (probe-out-supine contour based on the CBCT seed
cloud). As expected, the FEM inferred contours follow the same trend as seed movement: the
posterior region of the prostate has moved posteriorly near the midline, while the lateral sides of
the contour have moved medially. The lateral movement is more noticeable in the yellow
contours, which could be due to changes in the surrounding tissue between the supine and
lithotomy positions. Prostate volume change was + 0.5% in Fluoro-dosimetry and - 4.6% in
CBCT- dosimetry.
Figure 3.8: Axial (top) and sagittal (bottom) view of the average implanted seed displacement due to prostate deformation in different regions of the prostate, after probe removal while the patient is still in lithotomy position (blue arrows) and after the patient is set in supine position (red arrows). All arrow lengths are in mm. The scale used to display arrows is different from the scale of the prostate contour. Yellow dots represent the implanted seed locations for all the patients with a sample prostate contour overlaid on them.
A frame from the cine loop for one of the Group 1 patients is shown in Figure 3.10. As can be seen, the quality of the images is low and seeds are not clearly visible. Most of the seeds were blocked by the leg stirrup. In order to quantify the seed movement as the probe is retracted, the locations of one or two visible seeds, in the posterior section of the prostate, were tracked for each patient by manual identification in each frame of the cine loop scan. The seed displacement was 0.6 mm on average and 1 mm maximum. These data did not provide enough information for studying the prostate deformation and the FEM explained previously was used for this purpose.
Figure 3.10: A sagittal view of the prostate in a frame of a cine loop scan while retracting the ultrasound probe.

3.3.2 Dosimetric Assessment

Scatter plots and Bland-Altman plots of prostate dosimetric parameters D90%, V100% and V150%, comparing Fluoro- and CBCT-dosimetry, are shown in Figure 3.11 and Figure 3.12, respectively. The error bars on the Figure 3.11 show the total uncertainty, which is going to be discussed in section 3.3.3.
Figure 3.11: Scatter plots showing the correlation between prostate D90%, V100% and V150% values in CBCT- vs Fluoro-dosimetry. The linear regression fit (red line) is shown on each graph. The dotted line represents one-to-one correspondence. The error bars show the uncertainty of each dosimetric parameter due to prostate contouring variability and the seed localization uncertainty.
Figure 3.12: Bland-Altman plots showing differences of prostate D90%, V100% and V150% values between CBCT- and Fluoro-dosimetry. The middle line in each graph shows the mean of the differences. The upper and lower lines indicate the limits of agreement between two dosimetry methods defined by a 95% prediction interval of the differences.
Quantitative comparison of all prostate dosimetry quality parameters obtained from Fluoro-, CBCT- and standard of care Day 0 CT dosimetry are shown in Table 3.2. P-values were calculated based on the Wilcoxon signed rank test rather than the paired t-test as the differences of quality parameters calculated from the two methods were not normally distributed. The average value ± CI of the prostate D90%, V100% and V150%, obtained from Day 0 CT dosimetry, are 109.4 ± 6.0%, 93.6 ± 2.6% and 55.9 ± 5.9%, respectively. Comparison of urethral dosimetry parameters of D5%, D30%, D50% and V150% from CBCT- and Day 0 CT dosimetry are listed in Table 3.3. The average value ± CI of the abovementioned parameters, obtained from Day 0 CT dosimetry, are 148.3 ± 12.1%, 132.6 ± 9.0%, 121.6 ± 7.9% and 0.1 ± 0.1cc, respectively.
Table 3.2: Comparison of prostate dosimetric quality parameters obtained from Fluoro, CBCT and Day 0 CT dosimetry

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dosimetry Method</th>
<th>Difference* with Day 0 CT Mean ± CI† (p-value**) [min, max]</th>
<th>Absolute Difference* with Day 0 CT Mean ± CI†</th>
<th>Difference CBCT - Fluoro Mean ± CI† (p-value**) [min, max]</th>
<th>Absolute Difference CBCT - Fluoro Mean ± CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate D90% (%)</td>
<td>CBCT</td>
<td>-0.7 ± 5.4 (p = 0.84) [-17.9, 14]</td>
<td>7.3 ± 2.9</td>
<td>1.0 ± 3.4 (p =0.38) [-9.3, 9.2]</td>
<td>4.3 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>0.4 ± 6.0 (p =0.39) [-19.6, 16.7]</td>
<td>7.9 ± 3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate V100% (%)</td>
<td>CBCT</td>
<td>-0.1 ± 2.2 (p =0.79) [-5.1, 6.6]</td>
<td>3.0 ± 1.1</td>
<td>0.0 ± 1.0 (p =0.73) [-3.0, 3.2]</td>
<td>1.1 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>-0.1 ± 2.7 (p =0.68) [-8.2,8.2]</td>
<td>3.7 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate V150% (%)</td>
<td>CBCT</td>
<td>2.5 ± 4.6 (p =0.24) [-9.5,18.3]</td>
<td>6.4 ± 2.8</td>
<td>4.1 ± 2.9 (p =0.013) [-5.8, 10.3]</td>
<td>5.3 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>6.7 ± 5.4 (p =0.004) [-11.1, 23.8]</td>
<td>8.5 ± 4.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†CI: 95% confidence interval     *Difference with Day 0 CT: Day 0 CT parameter – Fluoro/CBCT parameter
**p-value based on Wilcoxon signed rank test
### Table 3.3: Comparison of urethra dosimetric quality parameters obtained from CBCT and Day 0 CT dosimetry

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dosimetry Method</th>
<th>Difference* with Day 0 CT Mean ± CI† (p-value**)</th>
<th>Absolute Difference* With Day 0 CT Mean ± CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra D5% (%)</td>
<td>CBCT</td>
<td>4.5 ± 8.2 (p =0.50) [-15.7, 39.7]</td>
<td>8.6 ± 6.8</td>
</tr>
<tr>
<td>Urethra D30% (%)</td>
<td>CBCT</td>
<td>3.5 ± 8.3 (p =0.59) [-14.5, 43.6]</td>
<td>8.0 ± 6.9</td>
</tr>
<tr>
<td>Urethra D50% (%)</td>
<td>CBCT</td>
<td>-0.1 ± 5.3 (p =0.79) [-10.9, 18.4]</td>
<td>6.7 ± 3.2</td>
</tr>
<tr>
<td>Urethra V150% (cc)</td>
<td>CBCT</td>
<td><strong>0.1 ± 0.1 (p =0.03)</strong> [0, 0.3]</td>
<td>0.1 ± 0.1</td>
</tr>
</tbody>
</table>

†CI: 95% confidence interval  
*Difference: Day 0 CT parameter – CBCT parameter  
**p-value based on Wilcoxon signed rank test

Analysis of the D90% for all twelve sectors of the prostate for both intraoperative dosimetry methods and the difference in the D90% for the two methods is shown in Table 3.4. The p-values suggest a statistically significant difference between the D90% of the two methods in the posterior sector of the mid-gland and in all four sectors of the apex. Sector analysis of the prostate V100% showed no significant difference between the two dosimetric approaches.
Table 3.4: Comparison of the D90% dosimetric sector analysis performed for the Fluoro and CBCT-dosimetry methods.

<table>
<thead>
<tr>
<th>Sectors</th>
<th>Dosimetry Method</th>
<th>D90% (%) Mean ± CI†</th>
<th>Difference (%) CBCT - Fluoro Mean ± CI† (p-value*)</th>
<th>Absolute Difference(%) CBCT – Fluoro Mean ± CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CBCT</td>
<td>89.8 ± 13.4</td>
<td>-0.2 ± 3.2 (p = 0.75)</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>90.0 ± 12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CBCT</td>
<td>105.3 ± 13.6</td>
<td>-1.6 ± 5.6 (p = 0.96)</td>
<td>7.1 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>106.9 ± 12.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CBCT</td>
<td>102.5 ± 10.9</td>
<td>0.8 ± 3.3 (p = 0.45)</td>
<td>4.2 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>101.7 ± 10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CBCT</td>
<td>107.5 ± 12.5</td>
<td>0.2 ± 2.9 (p = 0.79)</td>
<td>3.7 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>107.3 ± 12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CBCT</td>
<td>109.6 ± 9.6</td>
<td>1.9 ± 3.0 (p = 0.2)</td>
<td>4.0 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>107.7 ± 8.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CBCT</td>
<td>130.1 ± 9.6</td>
<td>3.4 ± 4.6 (p = 0.11)</td>
<td>7.0 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>126.8 ± 9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CBCT</td>
<td>129.9 ± 8.9</td>
<td>4.8 ± 3.0 (p = 0.006)</td>
<td>5.5 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>125.1 ± 8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CBCT</td>
<td>134.7 ± 9.3</td>
<td>4.1 ± 3.9 (p = 0.06)</td>
<td>6.1 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>130.7 ± 8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CBCT</td>
<td>117.1 ± 9.0</td>
<td>2.9 ± 3.0 (p = 0.048)</td>
<td>5.2 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>114.1 ± 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CBCT</td>
<td>130.6 ± 12.3</td>
<td>6.4 ± 4.6 (p = 0.017)</td>
<td>8.2 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>124.2 ± 11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CBCT</td>
<td>129.3 ± 13.5</td>
<td>8.1 ± 4.5 (p = 0.003)</td>
<td>9.2 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>121.2 ± 12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>CBCT</td>
<td>132.1 ± 12.5</td>
<td>6.5 ± 4.8 (p = 0.011)</td>
<td>8.5 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>Fluoro</td>
<td>125.6 ± 10.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†CI: 95% confidence interval
*p-value based on Wilcoxon signed rank test

The effect of prostate deformation on prostate dosimetric parameters in each of the two intraoperative dosimetry methods is compared in Figure 3.13. D90%, V100% and V150% of the whole prostate are calculated once with the TRUS prostate contours and once with the deformed contours, for each method. The average difference and average absolute difference between computed dosimetric parameter values are shown in Table 3.5.
Figure 3.13: Comparison of prostate D90%, V100% and V150% evaluated with the deformed TRUS prostate contour versus the undeformed contour. Fluoro-dosimetry parameters are shown in blue and CBCT-dosimetry parameters are shown in red. Least square regression line and its equation are shown for each dosimetry method with the corresponding color.
Table 3.5: The effect of prostate deformation on prostate dosimetric parameters in Fluoro and CBCT-dosimetry methods.

<table>
<thead>
<tr>
<th>Effect of prostate deformation</th>
<th>D90%(%) Mean ± CI†</th>
<th>V100%(%) Mean ± CI†</th>
<th>V150%(%) Mean ± CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoro-dosimetry Difference*</td>
<td>0.4 ± 0.6</td>
<td>0.1 ± 0.3</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>Absolute Difference*</td>
<td>0.6 ± 0.4</td>
<td>0.3 ± 0.2</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>CBCT-dosimetry Difference*</td>
<td>0.1 ± 0.6</td>
<td>0.3 ± 0.3</td>
<td>-0.8 ± 0.5</td>
</tr>
<tr>
<td>Absolute Difference*</td>
<td>0.8 ± 0.2</td>
<td>0.4 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
</tbody>
</table>

*Difference : Dosimetric parameter using deformed prostate contour - TRUS prostate contour
†CI: 95% confidence interval

3.3.3 Uncertainty Analysis

The seed localization uncertainty was found to be 2.30 ± 0.50 mm and 2.21 ± 0.59 mm for TRUS-fluoroscopy and TRUS-CBCT registration, respectively. This seed localization uncertainty resulted in 2% variation in the prostate D90%, 1.2% in the prostate V100% and 1.8% in the prostate V150% of the Fluoro-dosimetry method. The average standard deviations of D90%, V100% and V150% calculated with contours delineated by three RO’s on TRUS images and Day 0 CT images, were used to represent the contouring uncertainty for Fluoro- and Day 0 CT dosimetry, respectively.

The uncertainties associated with the prostate D90%, V100% and V150% due to seed localization and contouring, as well as the quadrature sum of the two uncertainties, are shown in Table 3.6, for Fluoro- and Day 0 CT dosimetry. The uncertainty in Day 0 CT dosimetric parameters due to seed localization was based on the study by De Brabandere et al. [99], which
showed that interobserver variability in seed localization on CT images results in uncertainty of 2.0%, 0.9% and 3.6% in D90%, V100% and V150%, respectively. The uncertainties associated with CBCT-dosimetry metrics were assumed to be the same as those of Fluoro-dosimetry, as the same prostate contour is used for both dosimetric approaches and the seed localization uncertainty is similar for both methods.

Table 3.6: Uncertainties associated with the prostate D90%, V100% and V150% due to seed localization and contouring. Total uncertainty for each metric is calculated from the quadrature sum of uncertainties due to seed localization and contouring.

<table>
<thead>
<tr>
<th>Uncertainty</th>
<th>Fluoro-dosimetry</th>
<th>Day 0 CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contouring</td>
<td>Seed localization</td>
</tr>
<tr>
<td>D90% (%)</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>V100% (%)</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>V150% (%)</td>
<td>2.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

3.4 Discussion

Two intraoperative dosimetry approaches were presented in this chapter and compared to the standard of care Day 0 CT dosimetry at our institution. Comparing the whole prostate dosimetric parameters, differences in D90% and V100% were not statistically significant between the dosimetry approaches. The differences in prostate V150% were statistically significant, being on average 4.1% higher in CBCT- and 6.7% higher in Day 0 CT dosimetry compared to Fluoro-dosimetry.
The uncertainty analysis performed in this study showed that the interobserver variability in prostate contouring has the largest contribution to the uncertainty in prostate dosimetric parameters. Based on our uncertainty analysis in Table 3.6, the Day 0 CT and either of the intraoperative dosimetry methods will agree within 12.2% about 95% of the time \( (2 \times \sqrt{4.0^2 + 4.6^2}, \text{ coverage factor } k=2 \text{ which is equivalent to } 95\% \text{ CI}) \) for D90% and 5.6% \( (2 \times \sqrt{2.0^2 + 1.9^2}) \) for V100% and 10.2% \( (2 \times \sqrt{2.8^2 + 4.3^2}) \) for V150%. The differences reported for D90% and V100% in Table 3.2 can be explained by these estimated uncertainties. Utilization of magnetic resonance-ultrasound [100] and magnetic resonance-CT [101], [102] fusion to assist in contouring may help reduce these uncertainties.

The differences in V150% between the dosimetry methods were slightly larger than expected on the basis of the uncertainty analysis. This may be a consequence of factors, such as the change in patient position between Fluoro- and Day 0 CT dosimetry, which may cause a slight compression of the prostate tissue (as also suggested by the volume decrease in FEM deformation) when moving to supine position. Additionally, there are other factors that contribute to uncertainty that were not specifically addressed in this work, such as dose matrix resolution, image spacing, and method of prostate contour interpolation between the slices, all of which are present in standard of care dosimetry, and can affect "small" volumes (including non-contiguous isodoses at higher dose levels, such as 150%) more than larger volumes. However, the differences in V150% values between dosimetry methods are unlikely to be clinically significant considering the ongoing changes to dosimetry due to factors such as edema, edema resolution and seed migration over time. Although TG-137 recommended that V150% should be \( \leq 50\% \) of the prescribed dose to avoid rectal and urethral toxicity, it is still controversial and
there is no general agreement on that [103]. Jones et al. demonstrated that it is the anatomic location of the 150% volume that is important rather than the percentage value [104].

The D90%, V100% and V150% of the two dosimetric methods showed high correlation, with $R^2 > 0.82$. The Bland-Altman plots show that the bias between the two dosimetry methods for D90% and V100% is negligible. However, CBCT-dosimetry produces higher values of V150% in comparison to Fluoro-dosimetry, which can be seen in Figure 3.12. This may be caused by the difference in patient position between the dosimetry methods. Considering these, performing either dosimetry method is likely to be as good as the other. Furthermore, the effect of prostate deformation on prostate dosimetric parameters was found to be very small. For both dosimetry methods, prostate D90%, V100% and V150% calculated using the unaltered TRUS prostate contour showed very high correlations with the corresponding values calculated using the deformed prostate contour. It may therefore not always be necessary to calculate the deformation in order to obtain adequate intraoperative dosimetry. However, this may not be true for all patients and all ultrasound probe users, as it is sometimes required to push the probe against the prostate to obtain acceptable image quality which can cause large prostate deformation and consequently affect prostate dosimetric parameters.

Dosimetric sector analysis of the prostate showed small variations in V100% between the two methods, however, D90% of sectors 7, 9-12 (posterior sector of the mid-gland and all sectors of the apex) were somewhat higher in CBCT- compared to Fluoro-dosimetry. The variation of D90% in the posterior regions is expected as the patient position was changed from lithotomy to supine, a transition that appeared to cause the implanted seeds in the apex to move slightly
toward the mid-gland. In addition, more variation is expected for D90% as compared to V100%. V100% produces a skewed distribution with an upper limit of 100% and a mean value approaching 100%, therefore it has less inherent variability when the mean is close to 100% than D90%, which ranges freely. A further explanation for the differences seen in some of the sectors may be that the apex and posterior prostate are in high dose gradient regions, therefore, small changes in the seed distribution can have relatively large effects on the dosimetry. The small volumes of each sector also make them more susceptible to dose variability with change in seed location or prostate shape compared to the larger whole prostate volume.

Seed localization accuracy and prostate contour delineation on ultrasound images is expected to suffer from some inherent geometrical distortion of the images [105], [106]. However, compared to other uncertainties that exist for dosimetric evaluation of the implant, such as interobserver variability of prostate contouring and prostatic edema, this geometric distortion is generally considered to be negligible and is not typically accounted for in practice, and was therefore also not considered in this thesis.

The effect of prostate edema on seed locations in all dosimetry methods used in this study should be the same, as all the X-ray images were taken after the implantation was completed, when the edema effect is considered to be at or near maximum [107]. The average post-registration residual distance between the common set of seeds in mid-implant and end-implant fluoroscopic images was found to be 1.7 mm in this study, which is an indicator of the impact of edema on seed locations. Any edema effects that were present were incorporated into the seed localization uncertainty by considering the post-registration residual distance between the common set of
seeds in Fluoro/CBCT and TRUS images. Furthermore, it was reported by Chira et al. [108] that prostate volume measured after the insertion of a few needles is not significantly different from the volume measured after the full implant.

The sagittal cine loop images provided poor contrast for seed identification. The presence of metal from leg stirrups and operating table as well as the patient’s pelvic bone in the path of the C-arm X-ray beam are the main contributing factors in degrading the image quality. Therefore, these images provided only a small amount of information about the motion of the prostate as the ultrasound probe is removed.

In both dosimetric approaches, prostate contours were initially obtained from TRUS images that were taken partway through the implant, and then deformed to account for the effect of probe removal and changes in patient position. Since the seeds are either inside or in close proximity to the prostate tissue, it is expected that the seed motion between the seed clouds corresponds to the motion of the prostate tissue. The approach used to infer the prostate boundary in the absence of the ultrasound probe is similar to Liu et al. [88], considering that the seed movements were used to deform the prostate contours. While a thin-plate spline mapping model was used in their study, a FEM was chosen for this work as it is a more common technique for modelling tissue deformation [109]–[111] and can also operate in real-time. If personalized biomechanical parameters were obtained from shear wave elastography in the OR, this model could be used to predict the prostate deformation for each patient specifically.
Prostate tissue can be considered as a near-incompressible material with a Poisson’s ratio of 0.49 [112]. It is assumed that the prostate tissue is slightly compressible or expandable due to factors such as fluid outflow or inflow from or into the organ or urethral spaces. In our deformation model, a 0.5% volume increase was observed due to removal of the TRUS probe and a 4.6% decrease was observed from lithotomy to supine position change, which may have been caused by a change in the mechanical forces from the surrounding anatomy between the two positions.

3.5 Conclusions

As the Fluoro-dosimetry method described in this chapter can be repeated at any time during the implant, the results demonstrate that the Fluoro-dosimetry approach is feasible for real-time intraoperative dosimetry. Furthermore, final evaluation of the implant can be performed using the CBCT method, before the patient leaves the operating room. This may eliminate the need for conventional Day 0 CT (if routinely performed), and also presents an alternative means of postimplant assessment where conventional Day 0 CT is not a practical option. Although the sample size used in this study, was small, the results suggest that prostate dosimetry parameters obtained from the Fluoro- and CBCT-dosimetry methods were in agreement with Day 0 CT dosimetry, within the limits of uncertainty associated with each method. Furthermore, the effect of prostate deformation due to the ultrasound probe was found to be negligible in this work, suggesting that whole prostate dosimetry can be performed without accounting for this deformation.
Chapter 4: Automatic Detection of Seeds in 3D Ultrasound Images

4.1 Introduction

4.1.1 Motivation

As discussed in the chapter 3, one way of achieving an accurate registration between the ultrasound images and the seed coordinates acquired via fluoroscopy is to base it on a set of common seeds identified on the two image sets partway through the implantation procedure. Seed visibility on ultrasound images becomes worse as the number of seeds increases, but is still reasonable on images taken partway through an implantation, when the number of implanted seeds is still relatively small. Nevertheless, even under these conditions, manual seed segmentation is tedious and time consuming and may not be reliable [113], [114]. Han et al. [114] evaluated the consistency of manual seed identification on TRUS images following completion of the implant by calculating the percent of bright spots identified by all four study investigators, to be from 8% to 33% (median: 20%). Additionally, in order to perform intraoperative dosimetry in real-time, the manual interventions of the whole process should be minimized. Therefore, automatic detection of the seeds on the ultrasound images would be preferable. However, this is also a very challenging task due to the small size of the seeds, scattering and shadowing effects, and similarity of the seed signals with those created by calcifications, as reported by several groups who have worked on this problem [115], [116].

It is frequently necessary to detect and identify objects of interest in medical images. This can be a labor-intensive and sometimes difficult task for clinicians. Artifacts may be present, and there may be a lack of clarity and/or contrast between the background and objects of interest.
Therefore, there has always been a great interest in automating such tasks and potentially also improving the accuracy of the results. In recent years, object detection problems have been approached by deep learning methods. These methods are being employed successfully in a growing number of applications in medical image analysis [117] and have reached human-level performance in many important visual recognition tasks [104] [105] such as detection of breast lesions in mammography [120] and ultrasound [121], microbleeds in brain MRI [122] and pulmonary nodules in PET/CT images [123]. Most of these methods are based on extracting salient image features using a convolutional neural network (CNN) and estimating the probability of the presence of an object, the object class, and a bounding box around the object based on those features.

Although all the abovementioned methods are based on CNNs, there are also differences between the various methods. In the general computer vision field, the number, size, and locations of the object(s) of interest are not known a priori. Therefore, a brute-force approach would be to apply the CNN on a very large number of locations in the image (possibly at different magnifications). However, this makes the computational cost prohibitive [124]. Different methods that have been proposed in recent years have tried to address this computational challenge. Some of the state of the art methods rely on identifying a small number of candidate bounding boxes based on the CNN-extracted features. The object detection is performed only in the candidate bounding boxes with high object probability, thereby reducing the computational cost [125]. Faster methods apply the object detection CNN on a coarse grid over the entire image, but these methods are typically less accurate [126]. To date, deep learning has been applied in the field of prostate brachytherapy to detection of the implanted seeds in CT
[127] and MRI images [128]. However, there have been no reports of deep learning approaches applied to seed detection on ultrasound images.

This chapter begins with an overview of neural networks. Then, an investigation of automatic seed localization in transrectal ultrasound data using deep learning methods is described. Briefly, this method employed a CNN model that was trained on 3D cubical sub-regions of TRUS images of the prostate implant, which are referred to as patches. A two-step coarse and fine approach was used in detecting seeds in the TRUS images. First, a trained CNN applied in a coarse sliding window approach detects the vicinity of a needle track, which contains seeds, spacers, and vestiges of tissue trauma caused by the needle. This is followed by a second trained CNN applied in a finer sliding window approach to detect seeds within the needle track. In addition, the results of the proposed automated method were compared with that of manual seed segmentation performed by an expert in TRUS image processing.

4.1.2 Overview of Neural Networks

4.1.2.1 Fully Connected Neural Network

Artificial neural networks are the core of deep learning. There are three types of layers in a typical fully connected neural network: the input layer, where data such as images or text are fed into the network, the hidden layer, where a combination of non-linear operations is performed on the information from the previous layers, and the output layer, which outputs the result of the process. An example of a simple neural network with one hidden layer is shown in Figure 4.1.
Each layer is composed of a collection of neurons (also called nodes) that operate together within a neural network. The operations done by each neuron are a simple weighted sum of the outputs of the neurons from the previous layer plus a bias value. The result is passed through an activation function which determines whether a neuron should be activated or not. Then, the output of the activated neurons in each layer is used as the input to the next layer.

To train a neural network, a training set that consists of pairs of inputs and their corresponding outputs is used. The goal of training a neural network is to find the appropriate values for the neuron weights and biases such that, for a given input, the desired output is achieved. The
optimal values for the connection weights and biases are obtained by performing feed forward and backpropagation processes iteratively.

The feed forward is a process in which the training data are fed into the neural network model and a prediction of the true or expected output is provided. For each training instance, a cost-function, which computes the error between the ground truth and the predicted result of the network, is calculated. Then, during a process called backpropagation, the error contribution from each connection is computed and connection weights and biases are updated to minimize the cost function. The commonly used loss functions are categorical cross-entropy or mean square error. The mean square function is often used for regression tasks, while the cross-entropy function is used for classification tasks. The equation of a cross-entropy function for a data size of m is given by:

\[
H = -\frac{1}{m} \sum_{i=1}^{m} \sum_{k=1}^{K} y_{k}^{(i)} \log(\hat{P}_{k}^{(i)})
\]  

(4.1)

where \(y_{k}^{(i)}\) is equal to 1 if the ground truth class for the \(i^{\text{th}}\) instance is \(k\); otherwise it is equal to 0, and \(P_{k}\) is the estimated probability of class \(k\).

The learning rate controls how much to change the model in response to the estimated error each time the model weights are updated. Finding a good learning rate can be tricky. If it is set too high, training may actually diverge, and if it is set too low, training will eventually converge to the optimum, but it will take a very long time. The number of passes of the entire training dataset that the network has completed is referred to as the epoch.
There are several types of activation functions such as Sigmoid \( f(x) = \frac{1}{1 + \exp(-x)} \) and Tanh \( f(x) = \frac{1}{1 + \exp(-2x)} - 1 \). However, currently the most commonly used activation function is the leaky Rectified Linear Unit (ReLU) activation function [129]. This function is defined as \( \text{LeakyReLU}_\alpha(z) = \max(az, z) \). \( \alpha \) defines how much the function “leaks”, it is the slope of the function for \( z < 0 \), as shown in Figure 4.2. It is worth noting that another main contribution of the activation function is introducing nonlinearity to the model; otherwise, the combination of linear functions applied at each node would result in a linear model capable of performing only linear predictions.

![Leaky ReLu](image)

**Figure 4.2:** Leaky ReLU function with \( \alpha = 0.1 \)

The Softmax function is another activation function that is only used for the output layer of networks used for classification. This function allows the output to be interpreted directly as a probability. The raw score output of the last layer of a neural network, which is called logit, is passed as an input to the Softmax function, which generates a vector of (normalized)
probabilities with one value for each possible class. The equation for the Softmax function is shown below:

$$\hat{p}_k = \sigma(Z)_k = \frac{e^{z_k}}{\sum_{j=1}^{K} e^{z_j}} \quad \text{for } j = 1, ..., K$$ (4.2)

In this equation, K is the number of classes, Z is a vector containing the scores of each class and $\sigma(Z)_k$ is the estimated probability of class k given the scores of each class.

4.1.2.2 Convolutional Neural Network

Convolutional neural network refers to a machine learning algorithm that emerged from the study of the brain’s visual cortex [130]. It was shown that many neurons in the visual cortex react only to visual stimuli located in a limited region of the visual field (local receptive field). While the receptive field of different neurons may overlap, the individual neurons may react to different things such as lines with different orientations. Moreover, some neurons react to more complex patterns that are combinations of the lower-level patterns. These observation led to the idea that higher-level neurons respond to the outputs of neighboring lower-level neurons.

CNNs perform very well in many computer vision tasks such as image recognition [131] and object detection [132]. The significance of a CNN compared to classic neural networks is the presence of the convolutional layers. A convolution is a mathematical operation that slides one function over another and measures the integral of their pointwise multiplication. This operation is particularly useful when the input of the neural network is an image. In a classic neural network, an image of size (n, m) would require n x m nodes in the input layer. This would lead to
a computationally intensive network. On the other hand, by applying the convolution operation to the image, we are extracting features from that image (such as edges), which are much smaller in size. The amount of movement between the application of the convolution matrix to the input image is referred to as the stride and is illustrated in Figure 4.3. The output of the convolutional layer is called the feature map.

Another building block of a CNN is pooling layer. The goal of the pooling layer is to further downsample the input image, while retaining the important features, in order to reduce the computational load and memory usage. Downsampling also makes the neural network model more tolerant to image shift. The most common approach used in pooling is max pooling, which takes the maximum value from sub-regions of the input image.
A typical CNN model is a combination of a few convolutional layers that is followed by a pooling layer. The image becomes smaller as it proceeds through the network while more feature maps are extracted from the image. The complexity of the output features in each layer is increased as we get deeper into the network. The initial feature maps are typically simple, such as edges, while output features of subsequent layers are more complex, such as textures. At the end, fully connected layers are added, after which a final output layer, such as a Softmax, generates estimated class probabilities.

A CNN model is trained similar to a fully connected layer. After the CNN model is trained, the performance of the model must be evaluated on a data set that the model has never seen before (test data set). If the neural network is performing well for its training set but cannot generalize its prediction to unseen examples, overfitting has occurred. A common approach to reduce overfitting in CNNs is data augmentation. In this technique, the size of the training data available for the learning algorithm is artificially increased. New training instances are generated from existing ones by slightly shifting, rotating or resizing every input image in the training set by various amounts, and the resulting images are then added to the training set. This makes the model more tolerant to the position, orientation and size of the object that is going to be detected in the image.

4.2 Materials and Methods

4.2.1 Data

Data sets from two different studies, described below, were combined and used in this work. TRUS RF data were used throughout as input to the deep learning algorithm. RF signal analysis-
Based methods, as compared to conventional B-mode images, have demonstrated higher accuracy in a number of studies [133], [134] of prostate tumor visualization. Although these studies were performed for prostatic lesion identification, the choice of using the RF signal in brachytherapy seed detection also seemed more reasonable as a large portion of the information is lost when B-mode ultrasound images are generated from the RF signal data. Where visualization was needed in this study, TRUS B-mode images were created from the collected TRUS RF data which are inherently registered to the RF data.

4.2.1.1 2018 Study

The 2018 study refers to the study described in chapter 3. Data from eight patients of Group 3, described in section 3.2.1.3, were used for this work. As mentioned before, model AgX100 $^{125}$I stranded seeds (Theragenics, Buford, Georgia) were used for implantation. Two types of strands are currently used at our center: TheraStrand and TheraSleeve. An image of both types is shown in Figure 4.4. As can be seen, the seeds and spacers are enclosed by a tubular membrane in the TheraSleeve configuration. This tube has a constant diameter along the strand. By contrast, spacers in the TheraStrand have a smaller diameter than the seeds, and the stranding material is a braided membrane that conforms to the seeds and spacers such that the strand diameter is slightly greater in the region of the seeds relative to the spacers. Most spacers are 5.5 mm in length, although a longer spacer (or several abutting shorter spacers) may be required in some strands by the treatment plan. Abutting seeds within a strand were not used in any of the treatment plans.
Figure 4.4: (a) Physical dimensions of the Theragenics AgX100 Iodine-125 brachytherapy seed (b) TheraSleeve (top) and TheraStrand (bottom) seed strands (note: the seeds in both the TheraSleeve and TheraStrand are identical)

Data from imaging interventions 3 and 4 (as described in chapter 3) were used for this work and are summarized below for ease of reference.

- Three to five 2D fluoroscopic images at 0, ±5 and ±10 degree angles around the patient's mid-sagittal plane, for the purpose of localizing the implanted seeds. These fluoroscopic images provided a useful guide for seed identification on the TRUS images for the purpose of creating a training set for the deep learning algorithm.
- 3D TRUS RF data using a BK Medical Pro Focus 3D ultrasound acquisition apparatus (described in section 3.2.1.2)
The abovementioned image sets were acquired after the seeds in four needles had been implanted. The four needles were intraprostatic, mainly in the anterior or middle of the prostate and reasonably well separated.

4.2.1.2 2010 Study

The 2010 study was also a research ethics board approved study (certificate number: H06-70146) carried out in 2010 and was aimed at improving the prostate brachytherapy procedure at our institution [87], [135]. Data from five patients of this study were used in this work. $^{125}$I model 6711 seeds in RAPIDStrand from Oncura GE Healthcare (Arlington Heights, IL) were used for implantation. RAPIDStrand was very similar to the TheraStrand shown in Figure 4.4.

Each patient received imaging interventions at the end of the procedure, after all seeds had been implanted, which consisted of:

1) Three 2D fluoroscopic images at 0, ±5 degree angles around the patient's mid-sagittal plane for the purpose of localizing all the implanted seeds.

2) 3D TRUS RF data using the 3D ultrasound acquisition apparatus (similar to the setup described in section 3.2.1.2).

A Sonix RP ultrasound machine (Ultrasonix Medical Corporation, Burnaby, BC, Canada) was used at the time of this study. The probe rotation was from -45 to 50 degrees and 270 frames were collected in one rotation. The frame size was $5 \times 5.5$ cm$^2$. 
4.2.2 Seed Detection Methodology

For seed detection, the collected TRUS RF data were first cropped to a region of interest that included the prostate and an area around it that could potentially contain needle tracks. In order to reduce the RF data matrix size and improve the processing time, the regions anterior and posterior to the gland were excluded since no seeds were present there. The proposed seed detection methodology consisted of two steps. The first step was to coarsely localize the needle tracks. This will be referred to as “needle path detection”. In the second step, a finer search was conducted within each of the detected needle tracks to find the implanted seeds. This step will be referred to as “seed detection”. CNN was used for both needle path and seed detection. The architecture of the network used for both steps was exactly the same, but different training sets were used in each step.

4.2.2.1 Training Set Creation

Since seed visibility is relatively poor on TRUS imaging compared to fluoroscopy, the gold standard for the seed locations on the TRUS data was acquired with the help of seed location information obtained from the corresponding fluoroscopic images.

For the 2018 study, the 3D locations of the implanted seeds had been determined from the reconstruction of the fluoroscopic images [94], from which a binary image was created. This, together with TRUS B-mode images, was exported to a commercially available image registration package (MIM Maestro, Cleveland, OH) and manually registered on the basis of a few unambiguously identifiable seeds. All of the seeds were then manually segmented on the B-mode images guided by the overlaid fluoroscopy seed locations. The centroid coordinates of the
seeds were used to define their locations. These locations were then mapped to the corresponding RF ultrasound data and used to create the seed patches (126 patches) for the training set.

For the 2010 study, a subset of seeds was localized on TRUS images through template matching, thresholding and spatial filtering (the details of which are explained in the paper by Moradi et al. [87]). These subsets of seeds were registered to the seed cloud of the completed implant obtained from 3D reconstruction of the fluoroscopic images, using matched needle tracks. The seeds on TRUS images that had correspondence with the fluoro seed cloud after registration were mapped to the corresponding RF ultrasound data and used to create the seed patches (112 patches) for the training set. The TRUS images of the 2010 study were crowded with >100 brachytherapy seeds as they were acquired at the end of the implant. Since the ground truth for the locations of only a portion of the implanted seeds was known, this data set could not be used for testing our proposed seed detection algorithm. TRUS images of the five patients from the 2010 study were used only to expand our training set, and testing of the CNN models was carried out on data from the eight patients in the 2018 study.

For the needle path detection model, the size of patches used was $4 \text{ mm} \times 9 \text{ mm} \times 30 \text{ frames}$. Seed patches captured an entire seed and a portion of the spacers on either side and were given a class label of one. Non-seed patches were given a class label of zero and were selected from the image background, excluding regions on the needle track. For the seed detection model, the size of the patches was selected to be $1.3 \text{ mm} \times 4.5 \text{ mm} \times 10 \text{ frames}$. Seed patches were chosen to encapsulate a seed only (class label = 1). Non-seed patches for this model were selected from inter-seed regions along the seed strand as well as background regions adjacent to the strands.
(class label = 0). A total of 238 seed patches were used in each model. The configurations of patches for both models are shown in Figure 4.5.

![Diagram of patch configurations](image)

**Figure 4.5: Definition of the patches used for training the neural network in the two models: (a) needle path detection model and (b) seed detection model, shown on a seed strand. Seed patches are shown in red and non-seed patches are shown in green. Non-seed patches for model (a) -not shown here- were selected from the image background, excluding regions on the needle track.**

### 4.2.2.2 Neural Network Architecture

The network architecture is shown in Figure 4.6. On the surface, it looks similar to the classic model of LeNet for handwritten digit classification [136]. However, modern elements and training and initialization strategies, including the weight initialization method proposed by He et al. [137], leaky ReLU activations [129] and dropout [138], were used. Activation functions determine the output of the neural network. Leaky ReLU activation was used in the deep neural network since it is computationally cheap and easy to implement. Dropout is a regularization
method that prevents neural network from overfitting. Both leaky ReLU activation and dropout technique improve the performance of the neural network.

![Image](image.png)

Figure 4.6: The proposed convolutional neural network architecture used for needle path detection and seed detection.

The network consists of four convolutional blocks. The first convolutional layer in each block uses a kernel size of $3 \times 3 \times 3$ and stride of 2, reducing the size of the feature map by a factor of 2 in each dimension. This is followed by two convolutional layers with the same kernel size of $3 \times 3 \times 3$ and stride of 1. All convolutional layers are followed by ReLU activation and dropout. The feature map of the last convolutional layer is vectorized and fed into a fully connected layer and followed by dropout. The output of the CNN is a two-element logit vector, which is passed through a Softmax function to yield the probability of the patch being identified as a seed or non-seed patch. The network was trained by minimizing the cross-entropy between the probability vector and the true class label vector using the optimization method proposed by Kingma et al. [139] with a batch size of four. Seed and non-seed patches were randomly shuffled and two patches from each group were fed into the CNN for optimization. During training, data
augmentation was performed by adding white Gaussian noise with standard deviation of 0.03, and by applying rigid translation and non-rigid elastic deformation to the patches.

The CNN models were trained for 10 epochs for needle-path-detection and 20 epochs for seed-detection. The models were not sensitive to the learning rate parameter, with values between $1 \times 10^{-6}$ and $1 \times 10^{-4}$ showing good results. Therefore, the learning rate was set to $1 \times 10^{-5}$. The model with the highest accuracy was selected for testing. Due to the small number of patients in the data set, a leave-one-out cross validation method was used. The model was written in Python using TensorFlow (Google, Mountain View, CA). The models were trained and tested on a Lenovo computer server that operated under Linux 4.4.0-143-generic x86_64 operating system and contained NVIDIA GP106 GPU.

### 4.2.2.3 Model Implementation

The trained needle-path CNN model was applied on RF images in a sliding-window approach, with a window of the same size as the needle path detection training patches, using a stride of 1/4, 1/8, 1/4 of the patch dimension in each of the three directions. The finer stride of 1/8 was chosen along the seed length as our goal was to detect the needle track. The image data from within each window position were fed to the CNN model, which generated a probability for classification as a seed. The end result was a likelihood image that was generated via averaging of the probabilities estimated with sliding windows described above. The likelihood image produced by the CNN was normalized in the range of 0 to 1 to produce the probability map. An example of the sagittal view of the probability map for a needle track in one of the patients is shown in Figure 4.7-a.
A binary thresholding filter was applied to the probability map to isolate regions with probability higher than 0.3. This threshold was determined empirically on the training data and was chosen primarily with the aim to maintain the bright spots on the needle track. This threshold may not necessarily be optimal for all patients or for a different dataset and in practice, the ideal would be to provide an option to change the threshold on a case by case basis.

Figure 4.7: Probability map inferred from the trained CNN for (a) needle path detection model and (b) seed detection model. White represents a probability of one and black represents a probability of zero.
The next course involved removing high-probability regions that existed far from the expected
needle paths. For that, a skeletonization algorithm [140] was applied to extract the 3D medial
axis skeleton of the higher probability regions. This provided a set of pixels representing the
curve-skeleton of the needle path. The 3D space was then divided into four sections (using the
center of mass of the output pixels) so as to have one needle in each region. A straight line was
fitted to the curved output of the skeletonization algorithm in each region using the Random
Sample Consensus (RANSAC) method [141]. This straight line was used to aid in localization of
the region containing the needle path. In order to limit the 3D space of the localized region that
contains the needle path and considering that the angle of needle splay is typically small, a
constraint was added to the fitted line. This constraint ensured that the angle of the outputted line
was less than 10 degrees relative to the Z-axis, which was oriented parallel to the transrectal
ultrasound probe (i.e. approximately along the patient’s superior-inferior axis and parallel to the
intended needle trajectories). Outlier points that were more than 5 mm away from the line were
assumed to be false positives and were removed. This 5mm limit was determined empirically
based on our data set, with the aim to capture any deviations due to needle curvature. The
detected needle tracks were then smoothed using a moving average filter.

To carry out the second step of the algorithm, the trained seed-detection model was applied only
on a region with a margin of 5 mm around the needle tracks and 2 cm beyond each end. The
seed-detection model was applied in a sliding-window approach, with a window of the same size
as its training patches, using a stride of 1/4 of the patch dimensions in all three directions. The
resulting likelihood image was normalized to produce the probability map, an example of which
is shown in the sagittal view in Figure 4.7-b. Then, a binary thresholding filter was applied to
extract regions with probability higher than 0.3. This threshold was also determined empirically. The center of mass of each group of connected voxels was calculated and identified as a seed candidate location. The overall workflow of the proposed seed detection algorithm is illustrated in Figure 4.8.

![Figure 4.8: Outline of the proposed seed detection algorithm](image)

**4.2.3 Human Performance**

Manual seed localization was performed on the eight images of the 2018 study in MIM software by an observer with several years of ultrasound image processing experience. Seed localization was performed twice by the same observer. In the first pass, the observer was asked to mark the positions of what appeared to be seeds, without a priori information about the number of
implanted seeds. The only prior knowledge was the number of implanted needles. This manual seed localization will be referred to as Method 1. In the second round, the number of implanted seeds for each patient was provided in addition to the number of implanted needles and this will be referred to as Method 2.

4.2.4 Performance Evaluation

To evaluate the performance of the seed detection algorithm and the manual seed localization methods, seed candidates that were within 2.5 mm (which is slightly greater than half of a seed length) distance from the gold standard centroid coordinate of the seeds along the needle path and 2 mm (this value was chosen based on consideration of the dimension of the training patch used and the size of the stride for window-sliding in seed detection model) away from it in the perpendicular direction, were considered as true positives. The rest were false positives. The performance metrics, precision, recall and F1_score (the weighted harmonic mean of recall and precision) [142] were computed for all the patients as:

\[
\text{Precision} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}} \quad (4.3)
\]

\[
\text{Recall} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}} \quad (4.4)
\]

\[
F1\_score = 2 \times \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \quad (4.5)
\]
4.3 Results

For the trained CNN seed detection model, the average value of precision was $78 \pm 8\%$, recall was $64 \pm 10\%$, and F1_score was $70 \pm 8\%$. The average values for false discovery rate and false negative rate were $22 \pm 8\%$ and $36 \pm 10\%$, respectively. The performance metrics for all the patients are shown in Table 4.1.

Table 4.1: Precision, recall and F1_score of the trained CNN seed detection model for the eight study patients

<table>
<thead>
<tr>
<th>Study patient number</th>
<th>Precision</th>
<th>Recall</th>
<th>F1_score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.61</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>2</td>
<td>0.86</td>
<td>0.67</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
<td>0.69</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>0.71</td>
<td>0.67</td>
<td>0.69</td>
</tr>
<tr>
<td>5</td>
<td>0.86</td>
<td>0.67</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0.75</td>
<td>0.56</td>
<td>0.64</td>
</tr>
<tr>
<td>7</td>
<td>0.78</td>
<td>0.50</td>
<td>0.61</td>
</tr>
<tr>
<td>8</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>Average ± SD*</td>
<td>0.78 ± 0.08</td>
<td>0.64 ± 0.10</td>
<td>0.70 ± 0.08</td>
</tr>
</tbody>
</table>

* SD = Standard Deviation

The results from the manual seed localization are shown in Table 4.2. The average value for false discovery rate and false negative rate were $44 \pm 9\%$ and $27 \pm 17\%$, respectively, for Method 1 and $30 \pm 12\%$ and $30 \pm 12\%$ for Method 2. Per patient, the manual seed localization took about 3 minutes in Method 1 and approximately 5 to 8 minutes in Method 2.
Table 4.2: Precision, recall and F1_score of the manual seed localization (Method 1: observer was not provided with any a priori information, Method 2: observer had a priori information about the number of implanted seeds for each patient)

<table>
<thead>
<tr>
<th>Study patient</th>
<th>Precision</th>
<th>Recall</th>
<th>F1_score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method 1</td>
<td>Method 2</td>
<td>Method 1</td>
</tr>
<tr>
<td>1</td>
<td>0.56</td>
<td>0.55</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.70</td>
<td>0.67</td>
<td>0.89</td>
</tr>
<tr>
<td>3</td>
<td>0.52</td>
<td>0.81</td>
<td>0.69</td>
</tr>
<tr>
<td>4</td>
<td>0.58</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>5</td>
<td>0.55</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>6</td>
<td>0.48</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>0.44</td>
<td>0.93</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>0.67</td>
<td>0.75</td>
<td>0.93</td>
</tr>
<tr>
<td>Average ± SD*</td>
<td>0.56 ± 0.09</td>
<td>0.70 ± 0.12</td>
<td>0.73 ± 0.17</td>
</tr>
</tbody>
</table>

*SD = Standard Deviation

The number of true positives and false positives obtained from the trained CNN model and manual seed localization methods are shown in Figure 4.9.
Figure 4.9: Bar plot of the true positive and false positive counts of identified seeds obtained from the trained CNN model and manual seed localization methods: Method 1 (the observer was blind to the number of implanted seeds) and Method 2 (the number of implanted seeds for each patient was provided to the observer).

The needle tracks obtained from the first step of the trained CNN model were compared to the gold standard in terms of their lengths and the positions of their ends. The gold standard length of the needle track is defined from the tip of its first seed to the end of its last seed. The histogram of needle track length error is shown in Figure 4.10 (negative values show that the detected needle track is shorter than the gold standard length). The average absolute value of errors is 6 mm. The distances between the superior ends of the detected and gold standard needle
tracks were also measured, as were the distance discrepancies at the inferior ends. The mean absolute difference was 4 mm both superiorly and inferiorly.

![Histogram of the detected needle track length error obtained from the CNN model](image)

**Figure 4.10:** Histogram of the detected needle track length error obtained from the CNN model (negative values show that the detected needle track is shorter than the gold standard length)

The total inference time for the trained CNN needle-path detection model was about 7 min for each patient and the inference time for the seed-detection model was about 1 min for each needle, leading to a total seed detection time of less than 15 minutes.

### 4.4 Discussion

Machine learning methods allow us to reduce human biases. In comparison to image processing based approaches which rely on specific assumptions, deep learning approaches have shown superior accuracy in object detection, classification and localization without needing strong assumptions [121]. The performance of deep learning methods may equal or even exceed human
performance. For example, it could be very challenging to identify the annotated area in the B-mode ultrasound image shown in Figure 4.11 as a seed, by human observation only. However, the proposed algorithm was able to identify this location as a seed on raw RF ultrasound images.

Figure 4.11: Sagittal view of a B-mode ultrasound image for one of the study patients where annotated areas shows an implanted brachytherapy seed.

On the other hand, Figure 4.12 shows an example of where the trained model did not detect a seed where one was expected on the basis of the fluoroscopic image to TRUS registration. However, this was not unexpected as there is no visible evidence of a seed at that location. The largest needle track length error in Figure 4.10 corresponds to this example.
Common object detection CNNs used in computer vision, such as the method proposed by Ren et al. [125], train a model to work on an entire image volume. A patch-based approach was used in this work for several reasons: First, given the small size of our training data (a total of 13 image sets containing 238 seeds), adopting a patch-wise approach will increase the number of available training instances. Secondly, unlike general object detection in computer vision where the size and orientation of the object of interest can vary greatly, in brachytherapy applications the size and orientation of the seeds in the image are largely constant. This is a useful piece of prior information that can be even more valuable considering our small data set. The proposed approach naturally takes this information into account by working with patches of suitable size. Lastly, a patch-wise model will be easy to apply on test images of arbitrary size in a sliding-
window approach, whereas a model that works on entire image volumes would restrict the dimensions of the admitted test images.

A two-step seed detection algorithm was proposed to get the best possible result with a reasonable computation time. The choice of the relatively large sliding window and stride size in the first step saved a lot of time without compromising the accuracy of our seed detection method, since the purpose at this point was to coarsely localize a limited 3D space for a more delicate search later. A finer search in the second step was required since the location of seeds had to be determined. However, the inference time for this step was low due to the small search space obtained from the first step.

As can be seen in Table 4.1 and Table 4.2, the CNN trained model has higher precision (lower false discovery rate) compared to the manual seed localization methods. In manual seed localization, Method 1, on average 29% (range: 6% to 70%) extra seed candidates were identified on each image as there were many bright spots in TRUS images that looked like a seed. This resulted in a high number of false positives and in some cases, a high number of true positives, as can be seen in Figure 4.9. Manual seed localization Method 2 showed that even with a priori information about the number of implanted seeds, the performance metrics are not necessarily better in all cases compared to that of the CNN model, which was not provided with any a priori information. Of note, precision and recall values are the same for each patient in Method 2. This is due to the fact that the number of identified false positive and false negative seeds were equal as the number of implanted seeds for each patient were provided to the observer in this method.
Furthermore, the proposed automated method estimates the probability of the seed presence in a small sub-window, whereas the human observer had the entire image context to infer from. Even under these conditions, in seven out of eight patients, both manual seed localization methods produced more false positives than the CNN model.

Other groups have explored seed detection in ultrasound data. In a study by Wei et al. [115], an algorithm based on image subtraction was used and a detection rate of > 95% was reported. However, their experiment was performed on agar phantom and chicken tissue, and not on a real patient where factors such as prostate deformation and patient motion come into play. Also, loose seeds, without any spacer, were used in the study by Wei et al. Considering that spacers produce ultrasound echoes, it is expected that seed detection on an ultrasound image where no spacers or stranded seed trains were used would achieve a better result. However, stranded seeds are preferred in many institutions due to reasons such as preventing migration of seeds to other body areas. Also, stranded seeds provide valuable a priori information for the seed detection algorithm such as higher certainty of a seed being along a line. In the work presented in this chapter, stranded seeds simplified the plan reconstruction as well as the registration step between fluoroscopic and TRUS image sets by maintaining the expected seed spacing within the seed trains.

Seed detection has also been investigated in similar imaging modalities such as photoacoustic imaging [143] and ultrasound imaging enhanced by electromagnetic tracking [144], but none of these methods are standard clinical practice and have not been tested on real patients in a clinical setting. Moradi et al. [87] applied a template matching-based approach on real patient TRUS RF
data from the 2010 study with the ultimate goal of intraoperative dosimetry and obtained low recall values, in the range of 10% - 43%. However, as mentioned previously, the images used in their study contained a higher seed density that causes more scattering and therefore lower image quality, which may have contributed to the lower recall. Acquiring the ultrasound when the number of implanted seeds is still relatively small, as was done in the 2018 study, provides an image set with sufficient quality for prostate boundary delineation as well as seed identification at that point.

In this study, seed detection precision was above 70% for all patients except patient #1. Of note, this patient had been implanted using TheraSleeve strands whereas TheraStrand was used for all other patients. It is suspected that the tubular membrane of the TheraSleeve strand could have altered the ultrasonic echoes from the seeds and spacers sufficiently (relative to the TheraStrand signals) to compromise detection based on a learning set derived almost exclusively from TheraStrand echoes. Consequently, fewer seeds were detected, and there were more false positives. Adding more samples to the training set from different patients, as well as developing separate trained CNN models for different strand types, will help to improve the performance of the proposed method. For example, data from different seed configurations in a strand, such as abutting seeds, which are not commonly used at our institution but are used elsewhere, could be added to the training set. This has not been studied in this thesis; however, it is expected that the patch-wise CNN model would work well for any configuration of seeds.

Recall values in this work showed that at least 50% of the seeds were detected for all patients. Although, on average 36% of the seeds were not detected, this will not be an issue for our
proposed method of prostate brachytherapy intraoperative dosimetry, where a subset of common seed locations in TRUS and fluoroscopic images is sufficient for registration of the two image sets.

As seen in this and related works, seed detection on ultrasound is challenging. In current clinical practice, TRUS imaging is not considered to be a suitable modality for seed detection, requiring supplementary imaging such as CT to be used for this purpose. Recent endeavors to detect brachytherapy seeds on CT images using deep learning based approaches [127] have indeed produced a high detection rate. However, brachytherapy seeds are specifically designed to produce good contrast with X-ray imaging modalities, so the seeds are easily detectable. Good results are therefore expected and have long been available using simple image processing based methods. Similarly, a recent study reporting high detection rates on MRI [128] (which has historically not been considered a good imaging modality for seed localization) made use of seed trains with markers specifically designed for detection on MRI. Such advantages do not currently apply to seed detection with ultrasound. Although a new $^{125}$I brachytherapy seed design, with several grooves on its external surface to enhance visibility on ultrasound images, was introduced [145], [146], it didn’t seem to gain popularity among clinicians. Due to the nature of ultrasound imaging, it is expected that even if we manage to enhance individual seed visibility on TRUS images, interference of ultrasonic waves from multiple seeds will continue to have adverse effects on seed detection, especially when the density of seeds in the image is high. Furthermore, prostatic calcifications and other echogenic structures, such as the spacers situated between the seeds, produce ultrasonic reflections that interfere with seed detection.
As described in chapter 3, because of the limited ability to detect seeds on ultrasound, the intraoperative dosimetry workflow developed for this thesis requires only a subset of the seeds to be detected partway through the implant. These are then registered to a complete set of seed locations obtained intraoperatively from fluoroscopic images. An example of this registration using only seeds detected by the trained CNN model is shown in Figure 4.13 for patient #1. All the TRUS-seeds are shown with red circles (larger red circles representing true positives, and smaller red circles representing false positives). As can be seen, in this case no correspondences to the final fluoro seeds were found for false positive seed locations (as identified from comparison with the gold standard seed cloud).
Figure 4.13: Registration of the seeds obtained from mid-implant TRUS images (red circle: 11 true positives are represented by large circle and 7 false positives by small circles) and final fluoroscopic images (blue circles). Corresponding seeds in the registration are connected with a black line. (0,0,0) represents the center of the seed cloud. X,Y and Z axes correspond to patient's Right-Left axis, Anterior-Posterior axis and Inferior-Superior axis, respectively.

4.5 Conclusion

A novel two-step approach was proposed to detect brachytherapy seeds in 3D ultrasound images, using machine learning. A CNN model was trained with 3D RF image patches to first detect needle tracks and then the seed locations within the needle tracks. The models were applied on test images in a sliding window approach with leave-one-out cross validation. The performance
of the method was evaluated by computing precision, recall and F1-score. The results were promising for registration purposes in intraoperative dosimetry. The overall-run time of this method is less than 15 minutes, while the entire implantation procedure takes about half an hour. Considering that the proposed seed detection algorithm will be implemented after the implantation of the first four seed strands, there would be enough time for running the algorithm while some or all of the remaining strands are being implanted, which makes this method clinically suitable. In conclusion, this method shows great potential in automating the seed detection in TRUS images, with a relatively high precision for clinical data.
Chapter 5: Conclusions

5.1 Summary

5.1.1 Seed Placement Uncertainty

Effective source placement is one of the challenges in prostate brachytherapy and if it is not implemented successfully, it can have adverse dosimetric consequences. The study performed on a cohort of 178 patients in our institution confirmed previous findings by others that seed strands are not always implanted to the intended depth, and that they tend to deviate and splay from the intended trajectory, especially in the anterior region of the prostate. These findings were also in agreement with the results of regional dosimetry studies reported by our institution [74], [75], which have consistently demonstrated underdosage in the anterior-superior prostate.

5.1.2 Development of Intraoperative Dosimetry Methods

The principal aim of this thesis was to develop an intraoperative dosimetry approach that utilizes equipment already available in the operating room, and that does not unduly increase the duration of the implant procedure. Thus, it was proposed to register the implanted seed locations obtained from planar fluoroscopic and/or CBCT imaging to the prostate boundary obtained from TRUS images, based on a common subset of seeds identified on the two image sets. The techniques developed during the course of this work demonstrated that prostate dosimetry based on actual seed locations could be evaluated within a reasonable time frame while the patient is still on the operating table, and could be repeated at stages during the implant, thereby enabling live adjustment of the treatment plan.
Prostate dosimetric parameters obtained from the proposed intraoperative dosimetry methods, TRUS-fluoroscopy and TRUS-CBCT dosimetry, were in agreement with standard of care Day 0 CT dosimetry results. While TRUS images are acquired in lithotomy position with the ultrasound probe in the patient's rectum, the results of this work demonstrated that the effects of both the TRUS probe and the patient position (lithotomy versus supine) on prostate shape and position could be accounted for by deformable registration with a finite element model that utilized movement of the implanted seeds as control points. In addition, it was seen that these deformations had only a small effect on prostate dosimetric parameters, and that it may not be necessary to correct for them in all cases and/or each time dosimetry is assessed. Each of the proposed intraoperative dosimetry methods has its own advantages and disadvantages, as follows.

5.1.2.1 TRUS-Fluoroscopy Dosimetry

The TRUS-fluoroscopy method can be done with the patient in lithotomy position. Therefore, it can be performed easily at multiple times during the implantation. It is noteworthy that patients with bilateral hip replacements who undergo PIPB may potentially benefit from the TRUS-fluoroscopic method for postimplant dosimetric evaluation of the implant, since standard of care Day 0 dosimetry is hampered by significant artifacts created on CT images by the artificial hips. These can hinder seed and prostate segmentation to the extent that dosimetric evaluation is impossible. Although not verifiable in our study population, it is expected that interference from hip prostheses could be avoided on the fluoroscopic images since they are acquired in a only narrow range of angles between the patient’s knees.
A technical disadvantage of the TRUS-fluoroscopy method is that acquiring fluoroscopic imaging from multiple views around the patient can be challenging, especially in the case of larger patients, because of the clearance required between the patient's knees, so the number of times imaging is repeated during a procedure would have to take this into account.

5.1.2.2 TRUS-CBCT Dosimetry

For TRUS-CBCT dosimetry, CBCT image acquisition with the equipment used for this work must be performed with the patient in supine position since there is not sufficient clearance for C-arm rotation in the lithotomy position. However, volumetric data is acquired in a single rotation of the C-arm and provides a reliable image set for seed identification. Although the change in patient position is not ideal in this case, this intraoperative dosimetry method still provides feedback to the physician that could be acted upon, if necessary, before the patient leaves the operating room. Because it is acquired with the patient is in supine position, the TRUS-CBCT method provides a value that is closer to the standard of care Day 0 CT dosimetry.

A disadvantage of the CBCT method is poorer tissue contrast than in conventional multi-slice CT, which does limit the ability to assess dose to organs other than the prostate. However, in the case of the urethra, which is the most affected normal structure in this procedure due to the high doses it receives (and which is also not visible on conventional CT in the absence of contrast), the presence of contrast material in the catheter at the time of CBCT imaging allows it to be identified and urethral dosimetric parameters to be obtained.
Dosimetry between TRUS-fluoroscopy and TRUS-CBCT was found to be very similar, suggesting that TRUS-fluoroscopy is suitable for intraoperative dosimetric assessment, while TRUS-CBCT dosimetry can be reserved for postimplant “final check” before leaving the OR. TRUS-CBCT dosimetry is equivalent to standard of care Day 0 dosimetry as long as rectal dosimetry is not required, with the advantage that the patient has not left the OR yet, so there is still a chance for implant modification if for some reason there is still concern at this point.

5.1.3 Automatic Seed Detection on TRUS Images

A two-step algorithm, where a trained CNN model first detects needle tracks and then finds the seeds within each track yielded higher precision (lower false discovery rate) compared to a trained human observer. The precision was sufficient for application to the methods developed in this thesis for registering TRUS images to Fluoro or CBCT, providing an additional automated step in the workflow for real-time intraoperative dosimetric analysis of the implant.

5.2 Contributions

The contributions of this thesis can be summarized as below:

- Conducting a clinical study, recruiting the eligible patients and collecting research data in the operating room
- Modifying and developing tools and a proposed workflow for real-time intraoperative dosimetric evaluation of the PIPB at BC Cancer-Vancouver.

Previously developed tools including a semi-automatic prostate segmentation on TRUS images [60], 3D reconstruction of multi-view fluoroscopic images [40], finite element model for prostate deformation [97] and a plan reconstruction software [72] were
combined to develop a workflow for intraoperative dosimetric assessment of the prostate implant. All the software was modified to fit this research project.

- Developing the algorithm to apply object detection CNN tools to the problem of seed detection on ultrasound images.

### 5.3 Future Works

The research work presented in this thesis has some limitations that need to be addressed. It is recommended [27], [33] that prostate, rectum and urethra dosimetric parameters be reported for all prostate brachytherapy implants. If the proposed intraoperative dosimetry methods are going to replace Day 0 CT dosimetry, all the recommended values should be reported. Although both intraoperative dosimetry methods were successful in evaluating the prostate dosimetry, only the TRUS-CBCT dosimetry method provided urethra dosimetric parameters. Therefore, TRUS-CBCT dosimetry has to be performed before the patient leaves the operating room.

Rectum dosimetry was not evaluated in any of the proposed intraoperative dosimetry methods. The rectum boundary was not visible on fluoroscopy or CBCT images, however, it can be estimated on TRUS images from the location of the TRUS probe. This was not investigated in this thesis, as it provides a very rough estimate of rectal dosimetry. However, investigating a method for accurate segmentation of the rectum on TRUS images can be a future research area for improving PIPB intraoperative dosimetry.

As mentioned in the Introduction, air-filled gel is sometimes used for visualization of the urethra on TRUS images, however, the scattering from the gel hindered the seed detection and degraded
prostate boundary visibility on TRUS images in our study. However, it would be possible to acquire a prostate ultrasound volume study with gel at the beginning of the procedure to obtain urethral contours that could be fused to the later mid-implant ultrasound images acquired for seed identification and prostate delineation. Future work could include developing such a method for contouring the urethra and including it in the deformable registration.

During the course of this research project, many advancements have emerged in machine learning techniques and their application in medical image analysis. Performance of the automated seed detection algorithm proposed in this thesis could potentially be improved by incorporating a priori information about the number of implanted seeds from the preplan, when applying the CNN model on a test image. The trained CNN model, in the current algorithm, predicts the probability of the seed presence in a small window without having the context of relative seed positions or the expected number of seeds in each image. The model prediction could potentially be improved if this a priori information is utilized.

The prostate segmentations on TRUS images are currently performed semi-automatically using an in-house developed software. Recently, a CNN based method was developed for accurate automatic segmentation of the prostate in TRUS images [147]. This new method could be incorporated into the intraoperative dosimetry workflow, to automate the whole procedure. As mentioned earlier in this thesis, MRI is the gold standard for prostate delineation; therefore, preimplant MRI, if available, can be used to assist in prostate delineation on TRUS images as well.
The outline of a potential workflow for intraoperative dosimetric evaluation of PIPB using the methods developed in this thesis is presented in Figure 5.1.

![Diagram of workflow](image)

**Figure 5.1: Outline of a workflow that could be implemented using the tools developed in this thesis for intraoperative dosimetric evaluation of permanent implant prostate brachytherapy.**

TRUS RF data are acquired after seeds from a few needles are implanted. Implanted seed locations can be obtained in less than 15 minutes with the proposed CNN model algorithm described in chapter 4 [148]. Also, B-mode images are created from the TRUS RF data for prostate boundary delineation. The initial prostate boundary can be obtained with the semi-automatic prostate segmentation software [60] currently being used at our institution. All these
processes are performed while the radiation oncologist is continuing with the implantation procedure. After the implant is partially completed, fluoroscopic imaging in lithotomy is performed, and seed locations obtained from the fluoroscopy reconstructions are registered to the prostate boundary based on the common seeds identified on both TRUS and fluoroscopy. This step is facilitated by the plan reconstruction software [72] that finds the seeds corresponding to each strand and labels the strands according to the assigned needle number in the treatment plan. As a result, the seeds corresponding to the strands implanted at the time of TRUS imaging can be identified in the full implanted seed cloud, which facilitates the registration of the TRUS-fluoroscopy. The implant can be assessed at this point, and adjustments to the treatment plan made if necessary. These steps could be repeated at the discretion of the physician at any stage during the implantation of the remaining needles. Upon completion of the implant, they can again be repeated, with CBCT in the supine position (in place of or supplementary to the fluoroscopy reconstruction) also being a practical option at this point.

As with any intraoperative dosimetry approach, an additional computer would be required in the operating room, with treatment planning software such as VariSeed installed on it. The implanted seed locations, along with the prostate contours, would be imported to the TPS to visualize isodose values superimposed on the prostate contours. This same software would also be used to make adjustments to the treatment plan if required.

It is expected that workflow for intraoperative assessment of the PIPB dosimetry proposed in this thesis will add some additional time to the procedure in the OR. Average time currently spent for implantation solely is about half an hour, which can vary due to factors such as the number of the
needles required or how fast the RO is. The seed identification and prostate contour delineation on mid-implant ultrasound images take about 15 minutes but are required only once during each procedure and at the same time the implantation can be continued. Any fluoroscopic image set taken afterward to assess the dosimetry of the implant will add about 5-7 minutes to the procedure as identification of seed locations, registering them to the prostate contour, and exporting them to the TPS is relatively quick. After evaluating the dosimetry, the RO decides whether to adjust the treatment plan or continue with the current plan. Obviously, any modification to the treatment plan and its subsequent dosimetric evaluation will add some additional time to the procedure. Nevertheless, implementing the proposed workflow will potentially have the benefits associated with intraoperative dosimetric evaluation of the implant, as reported by others [66].

Duration of the proposed workflow will not be as long as intraoperative planning where a treatment plan is created in the OR, as in our case a treatment plan is created beforehand and only minor adjustment will be applied to the treatment plan if deemed necessary. Still, we desire to limit the added time to take images and adjust the plan. Therefore, as a future research direction for this project, an optimization algorithm can be developed to modify the treatment plan at any stage during the implantation and determine the ideal locations for the remaining needles based on the dosimetry distribution desired by the RO.

Finally, a clinical study to explore implementation of the proposed workflow in real-time in the OR should be conducted. In addition to evaluating the logistics of the intraoperative workflow,
dosimetric outcomes would have to be assessed and compared to Day 0 CT dosimetry before transitioning to a fully intraoperative imaging approach.
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