Characterization of Implanted Seed Orientation and Displacement Dynamics with Application to the Design of Non-Uniform Source Strength Treatment Plans for Prostate Brachytherapy

by

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Abstract

Low dose rate prostate brachytherapy is one of the most effective treatments for prostate cancer currently available. It involves the implantation of approximately one hundred small radioactive sources, or ‘seeds’, into the prostate gland. This is accomplished by depositing the seeds transperineally via 16-30 long needles. In British Columbia, over three thousand patients have been treated since 1998 using this technique, and fewer than 10% have suffered a recurrence to date.

One of the principal challenges in low dose rate prostate brachytherapy is the limited reliability with which precise doses to the prostate and surrounding organs can be achieved. This is due both to the difficulty in accurately delivering the seeds to their planned positions, as well as movement of the seeds in the post-implant period during the resolution of procedure-induced edema. This uncertainty can lead to undetected deficits in the dose necessary to control the cancer. As patients with more advanced disease are being considered for brachytherapy, these deficits may have greater consequences on oncological outcomes. Treatment uncertainty also increases the risk of side effects, which have the potential to be severe.

The overall aim of this thesis is to improve the scope and accuracy with which the dose distribution of stranded seeds can be measured after implant. This involved the development of an algorithm to uniquely identify seeds in post-implant CT data, along with a method to determine their orientation to improve dosimetric accuracy. An analysis of the displacement and migration patterns of seeds in the interval during the resolution of prostate edema was also undertaken. These results identified dosimetric deficiencies and modes of seed loss which have the potential to be rectified by the use of implants containing seeds of non-uniform strength (‘mixed-activity’ implants). Such treatments use fewer needles and may also reduce the incidence of treatment related urinary morbidity. Although the concept of mixed-activity implants is not novel, the algorithm developed to identify seeds after implant enables the post-implant assurance of their dosimetric quality in a clinically feasible way. This thesis concludes with a study investigating the dosimetric benefits of mixed-activity implants.
Preface

The research contained in this thesis was primarily designed and undertaken by the author. Two published manuscripts were derived from this work. The author was in both cases responsible for the production of the manuscript, with the feedback and comments of his co-authors. Drs. Ingrid Spadinger and Tim Salcudean provided technical guidance and clinical context, including their thoughts on acceptable accuracy, performance, and applications of the research. Dr. James Morris’ experience in brachytherapy implants was invaluable for setting clinically meaningful research goals, as was his assistance in contouring. The research conducted in this study was undertaken under the approval of a research ethics board, REB number H07-02680.

A version of Chapter 2, titled “Prostate brachytherapy postimplant dosimetry: Automatic plan reconstruction of stranded implants” was published in Medical Physics in 2010, co-authored with Drs. Spadinger, Usmani, Morris, and Salcudean. The development of the algorithm that is the subject of this chapter was motivated by a research project of Dr. Usmani, who was a radiation oncology fellow at the BC Cancer Agency when the project was initiated. Dr. Usmani sought to test the hypothesis that strands underwent systematic inferior migration between the day of the implant and a month afterward, which required a method to identify the same strands in each image set. The design, implementation, testing, and clinical translation of this method were all done by the author.

A version of Chapter 3, titled “Prostate brachytherapy postimplant dosimetry: Seed orientation and the impact of dosimetric anisotropy on stranded implants” has been accepted for publication in Medical Physics, but is not yet in print. It was co-authored with Ms. Rosey Rasoda, and Drs. Spadinger, Morris, and Salcudean. The author’s contribution to this work was proposing the initial idea, developing and implementing the spline-fitting code, creating a system to integrate orientation uncertainty into the dose calculation, and all testing and analysis of data. A GPU-accelerated method to efficiently calculate the dose distribution from angulated seeds was also developed by the author. Ms. Rasoda was an engineering co-op student who assisted in performing and validating plan reconstructions, contributed to the development and debugging of the early spline-fitting code, and worked on the graphical user interface for clinical translation.
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<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
</tr>
<tr>
<td>AAPM</td>
<td>American Association of Physicists in Medicine</td>
</tr>
<tr>
<td>ABS</td>
<td>American Brachytherapy Society</td>
</tr>
<tr>
<td>AIQ</td>
<td>Anterior Inferior Quadrant</td>
</tr>
<tr>
<td>AL</td>
<td>Anisotropic Linear</td>
</tr>
<tr>
<td>ASQ</td>
<td>Anterior Superior Quadrant</td>
</tr>
<tr>
<td>AUR</td>
<td>Acute Urinary Retention</td>
</tr>
<tr>
<td>BCCA</td>
<td>British Columbia Cancer Agency</td>
</tr>
<tr>
<td>BDFS</td>
<td>Biochemical Disease Free Survival</td>
</tr>
<tr>
<td>CI</td>
<td>Conformity Index</td>
</tr>
<tr>
<td>CSS</td>
<td>Cause-specific survival</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
</tr>
<tr>
<td>DTA</td>
<td>Distance-To-Agreement</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
</tr>
<tr>
<td>Dx</td>
<td>Maximum dose received by at least x percent (or cubic centimetres where indicated) of the prostate volume, unless prefixed by ‘U’ or ‘R’, which indicate urethral or rectal measurements.</td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiation Therapy</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HDR</td>
<td>High Dose Rate</td>
</tr>
<tr>
<td>IE</td>
<td>Isotropic Exponential</td>
</tr>
<tr>
<td>LDR</td>
<td>Low Dose Rate</td>
</tr>
<tr>
<td>MD</td>
<td>Minimum Distance</td>
</tr>
<tr>
<td>mPD</td>
<td>Minimum Peripheral Dose</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>PIPB</td>
<td>Permanent Implant Prostate Brachytherapy</td>
</tr>
<tr>
<td>PIQ</td>
<td>Posterior Inferior Quadrant</td>
</tr>
<tr>
<td>PO</td>
<td>Pooled Observer</td>
</tr>
<tr>
<td>PSQ</td>
<td>Posterior Superior Quadrant</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>RPE</td>
<td>Relative Position Error</td>
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</tbody>
</table>
RDE  Relative Dosimetric Error
RV  Rectal Vx (see Vx)
TG  Task Group
TPS  Thin Plate Splines
TRUS  TransRectal UltraSound
UDx  Urethral Dx (see Dx)
Vx  Volume of the prostate receiving more than x percent of the prescription dose, unless prefixed by ‘U’ or ‘R’, which indicate urethral or rectal measurements.
Acknowledgements

Few students will have been as fortunate as I to have had at my fingertips such a wealth of expertise in engineering, physics, and oncology. Fewer still will have enjoyed the latitude afforded to me in my endeavors, or the satisfaction of personally translating that research into clinical practice. I offer my abiding thanks to my committee members for the commitment of their time and expertise to this project, and the students and colleagues who have been my companions and friends in this undertaking. Lest this become a memoir, I cannot acknowledge all of the individuals around whom this work coalesced, with the necessary exception of the following: Sara Badiei, Alanah Bergman, Daniel Came, Rustom Dubash, Brad Gill, Ron Horwood, Mira Keyes, Vince Lapointe, Julio Lobo, Sara Mahdavi, Marie-Pierre Millette, Ante Mestrovic, Rosey Rasoda, Tony Teke, Nawaid Usmani, and Conrad Yuen. I would also like to thank the Prostate Cancer Foundation of B.C. for their generous grant-in-aid.

I am indebted to the perspicacious Tim Salcudean for his efforts as my PhD supervisor. His ability to resolve the crux of a research problem moments after its introduction must be seen to be believed. Also, no one who finishes a PhD can fail to admire the fortitude of those who pursue the grants which underwrite the entire endeavor. Although the process is a perennial frustration, it should not go thankless or unrecognized by the students who are its principal beneficiaries. So thank you, Tim!

To Jim Morris I credit the contraction of a Swiftian indignation for lackadaisical science, and the sincere wish never to have my work as its subject. I have immensely enjoyed our colourful lunchtime ‘research meetings’, which have shaped my understanding of the field, and the practical quandaries of clinical research. Jim’s mentorship has facilitated research opportunities and discourse with some of the most respected clinicians in the field. You want no other man introducing you at a conference banquet.

Every aspect of this thesis bears the indelible influence of Ingrid Spadinger, on whose quiet competence the brachytherapy program itself rests. Where this work falls short, it is entirely despite her acuity, succinctness, and rigorous attention to detail. She is a consummate medical physicist, and to say it has been a singular honour to train with her still feels miserly of my regard. I hope that in return I have imparted the need to occasionally close her door to students, this being the only practice in which I have identified deficiency.

Finally, to my family, for their enduring presence and support… I must concede the insufficiency of this medium and trust in paralipsis to articulate the extent of my gratitude.
1 Introduction

1.1 Clinical Background

1.1.1 Incidence and Impact of Prostate Cancer

A common rule of thumb is that the probability of a man having prostate cancer, as a percentage, is roughly his age minus ten. In 2011, an estimated 25,500 new cases of prostate cancer will be diagnosed, and 4,100 men are expected to die as a direct result of the disease in Canada. As in the United States, prostate cancer has the highest rate of incidence of any cancer in Canadian males, and histological evidence of prostate cancer has been detected during autopsy at rates which suggest that the majority of men eventually acquire the disease. The advent of the prostate specific antigen (PSA) test, which is easily administered but lacks specificity, has resulted in a sharp increase in the number of men being treated for the disease. However, the long natural history of prostate cancer and the difficulty in distinguishing between indolent and aggressive disease has created an environment where post-treatment quality of life plays a large role in how the physician and patient choose to manage the disease. At the British Columbia Cancer Agency (BCCA) patients who present with prostate cancer that has advanced beyond very low-risk disease are encouraged to pursue curative (‘radical’) treatment. The three main options are the surgical excision of the gland (radical prostatectomy), external beam radiotherapy (EBRT), and permanent implant prostate brachytherapy (PIPB).

1.1.2 Prostate Anatomy

The prostate is a walnut-shaped gland which weighs approximately 7 - 16 g in the healthy individual. It tends to grow with age, commonly resulting in urinary symptoms after age 50. The prostate can be divided into three zones, shown in Figure 1.1. The transition zone is primarily smooth muscle, and accounts for approximately 5% of the volume. The central zone comprises 25% of the prostate, has the greatest density of stroma, and a complex architecture of ducts and glands. The anterior region has a marked lack of glandular structures, and is primarily fibromuscular stroma. The peripheral zone comprises the remainder of the gland, where the majority of prostate cancers arise. The superior aspect of the prostate is referred to as the ‘base’, and the inferior aspect as the ‘apex’. The prostate does not have a capsule proper, but is surrounded by a fibromuscular layer that is most prominent around the base and lateral borders. In the apex, the gland blends into the musculature of the pelvic floor.

The bladder sits superiorly to the gland. The bladder neck often protrudes into the anterior base as it transitions into the prostatic urethra, which runs anteromedially through the gland, exiting in the anterior apex as it passes through the external urethral sphincter. The seminal vesicles lie on the superoposterior aspect of the gland, and the rectum passes
adjacent to its posterior boundary. The neurovascular bundles run along the posterolateral aspects of the gland. These innervate the corpora cavernosa and are involved in erectile function.

1.1.3 Diagnosis, Staging, and Risk Stratification

Suspicion of prostate cancer usually begins with the clinical presentation of urinary symptoms, the presence of masses during digital palpation, or the detection of an elevated PSA concentration. Clinical symptoms include urgency, a weak urine stream, and nocturia, although these symptoms are often the result of the benign swelling of the gland over the course of normal aging, and are not specific to the disease. Digital rectal examinations (DRE) are a routine part of screening in men over the age of 50, during which cancerous tissue may present in the form of hard nodules or noticeable asymmetry in the gland. In most cases, symptoms or a suspicious result during the digital examination will lead to the physician ordering a PSA test.

The development of prostate specific antigen (PSA) as a marker for prostate cancer began in the 1970s. It was FDA approved for monitoring treatment response in 1986, and for diagnostic screening in 1994. PSA is a naturally occurring protein produced exclusively by epithelial cells in the prostate. It aids in the production of semen, and is present at some concentration in all healthy males. Normal concentration ranges are age-specific, and tend to increase with age. Concentrations of 2.5 ng/ml and below are fairly typical in 50 year old men, and increases of approximately 1 ng/ml per decade of life after that are unremarkable. However, although moderate increases may be the symptoms of benign hypertrophy of the gland, increases above concentrations in the range of 3-4 ng/ml have been correlated with the advancement and aggression of disease. The positive predictive value for prostate cancer given a PSA concentration of
>4 ng/ml is ~30% (30% of such patients have prostate cancer), and the negative predictive value concentrations below this threshold is ~85% (85% of such patients do not have prostate cancer).

Several additional metrics have been proposed to improve the sensitivity and specificity of the PSA test. One measure is derived from trends in PSA concentration over time - the PSA velocity. Another is the ratio of free-to-total PSA, which is generally lower in patients with prostate cancer. Both assays are recommended by the American Urological Association’s best practice guidelines as a part of the diagnostic process. Higher PSA velocities prior to diagnosis have been associated with more advanced stage, grade, time to disease recurrence, and a lower likelihood of treatment success. However, its utility has recently been called into question by the results of a pair of large trials in which PSA velocity added little to no value over absolute PSA measurements alone. The utility of free-to-total PSA in clinical decision making is similarly controversial because it only marginally improves specificity.

Abnormal DRE or elevated PSA levels typically provoke a histological evaluation of tissue, involving a six to twelve core tissue biopsy, which is commonly guided by transrectal ultrasound (TRUS). A pathologist is consulted to assess the samples and make the diagnosis of cancer. The pathologist quantifies the progression of the disease with a Gleason score. The Gleason grading system was developed in the 1960’s by Donald Gleason, and is based on stratifying cancers according to patterns in the macroarchitecture of the tumor cells. A scale of one to five describes the degree to which the glands are differentiated, how they are clustered, and the patterns with which they infiltrate the adjoining stroma. Higher pattern grades indicate a greater progression of the disease. The score is typically reported by summing the individual scores of the grades of the two most prominent patterns in the biopsy samples. Thus, a score of $4 + 3 = 7$ implies that the most prominent pattern had a score of 4, and the second a score of 3. The Gleason score is a measure of tumour aggressiveness, and patients with lower scores typically are more likely to have their disease confined to the gland, and respond more favorably to treatment.

Prostate cancer is staged in accordance with the American Joint Committee on Cancer TNM (Tumour, Nodes, Metastases) system. Physical results from the digital rectal exam, which may be supplemented by radiological evidence, are used to stage the tumour from T1 to T4. Higher stages indicate more advanced disease and commensurately lower rates of survival. Subcategories at each level are indicated with a suffix: a, b, or c. In the prostate, T1 disease designates a prostate with a normal result on digital rectal examination. Palpable masses or nodules, but no obvious extraprostatic extension signifies T2 disease. At stage T3, extraprostatic extensions of the tumour are present, and by stage T4, the surrounding organs such as the bladder, rectum and pelvic wall may be involved. The ‘N’ and ‘M’ designations serve to describe the spread of the disease to local lymph nodes, and the existence of metastases.
The stage, Gleason score, and serum PSA are used to stratify the patient into prognostic risk categories. There are a variety of different risk stratification schemes, including the D’Amico stratification, the prognostic grouping in the 2010 TNM system, and the National Comprehensive Cancer Network (NCCN) guidelines. Low risk factors include PSA concentrations less than 10 ng/ml, Gleason scores less than 7, and localized disease (<T3). The various classification systems differ principally in how intermediate-risk patients are characterized.

1.1.4 The Goals of Treatment

To the majority of patients facing prostate cancer, the most important measure of treatment success is the subsequent risk of dying from cancer. This risk may be estimated by looking at populations of treated patients and assessing the proportions that have died at a particular time as a direct result of their disease. This particular form of mortality is called cause-specific mortality (CSM), and its converse is cause-specific survival (CSS). Importantly, CSS censors patients who pass away due to other causes, which typically dwarfs the number of cause-specific deaths in the demographic of prostate cancer survivors. Survival is traditionally defined at 5-year intervals, and is estimated by the application of statistical tools such as Kaplan-Meier analysis.

The difficulty with adopting CSS as an endpoint for evaluating treatment is that the natural history of low to intermediate risk prostate cancer is long, and by the time sufficient follow-up data on treated populations has been acquired, the technology and techniques associated with the treatment are often obsolete. Also, because most patients do not die of their cancer, very large patient cohorts are often necessary to identify enough cancer-specific events to generate reliable statistics. Consequently, more timely endpoints such as local recurrence rates, or the rates of progression to metastatic disease are routinely used.

Unfortunately, once local or metastatic recurrences have been detected, the outlook for the patient is bleak. Prostate cancer survivors are fortunate in that clinical progression of their disease is often preceded by rising trends in post-treatment PSA scores. When this happens, the patient is said to have suffered biochemical failure, which is an early indication that salvage therapy may be necessary. The current consensus definition of biochemical failure for radiation therapy is a PSA concentration that exceeds 2 ng/ml above the post-treatment nadir. In brachytherapy, failures are often audited for the so-called ‘PSA bounce’, a phenomenon wherein the patient may exhibit a transient increase above nadir, that, while technically triggering failure, typically declines shortly afterward with no excess risk of subsequent progression.

Biochemical failure has been found to antedate metastatic spread and subsequent mortality by a median of 8 and 13 years, and time to biochemical failure and PSA doubling time have been associated with greater...
risk of CSM in a randomized trial\textsuperscript{24}. This makes biochemical failure a valuable intermediate endpoint in the evaluation of treatment efficacy that serves as a means of identifying patients who may need salvage therapy. Studies of the outcome of prostate cancer patients often report results in terms of the rates of biochemical disease-free survival (BDFS): the proportion of patients living at risk of biochemical failure at a particular interval after treatment.

The use BDFS as an endpoint by which to compare different treatments is somewhat controversial, as the impact of failure on subsequent CSS may be modality-dependent. Its value as a surrogate endpoint has also been questioned because many patients have competing morbidities that may have a greater bearing on overall survival at the time of failure\textsuperscript{25}. Nonetheless, the clinical reality is that biochemical failure typically triggers salvage treatments with significant morbidity, such as androgen deprivation, and patients who remain free from biochemical failure have a higher quality of life\textsuperscript{26}.

1.1.5 The Effects of Screening

The PSA test has dramatically reshaped the profile of the typical prostate cancer patient. However, the value of routine PSA screening is unclear. Although early studies in Canada and Austria reported an improvement in CSS, the conclusions of two large random prospective trials in Europe and the United States have been more ambivalent\textsuperscript{27,28,29}. The European trial reported a 20\% decrease in the relative risk of death from prostate cancer in the screened group at a median follow-up of 9 years, but estimated that an astonishing 1410 additional screening procedures and 48 treatments are necessary to reduce the number of prostate cancer specific deaths by one. Meanwhile, the American study found no significant mortality benefits to screening at a median follow-up of 13 years, although the incidence rate in the population that received screening was 12\% higher. However, the confidence intervals were wide, as only 540 and 174 prostate cancer deaths were recorded in the American and European studies respectively. These results must also be interpreted in conjunction with the inevitable limitations inherent in large multi-centre studies. The confounding effects of contamination of the control groups with screening external to the study, variations in protocol between centres, and the differences in the management of cancer after detection between study arms may have obscured the impact of screening in the data. To date, quality-of-life endpoints, which might help to guide the decision making process for patients who are at lower risk of dying from their disease, remain forthcoming.

The lack of conclusive results means that the debate is likely to continue in the near future, with some physicians advocating routine screening, and others preferring to utilize PSA only for diagnostic confirmation and treatment evaluation and follow-up. Initially, a number of influential professional and patient advocacy groups such as the American Cancer Society and Canadian Urological Association recommended routine screening\textsuperscript{30}. However, the standard of care is shifting. As of a 2010 update, the
American Cancer Society joined its Canadian, British and Australian counterparts in revising its position on this issue to advocate instead for patients to make an informed, individual decision about participating in screening\textsuperscript{30,31}. Consistent with these recommendations, British Columbia does not perform routine population screening, and patients are advised to weigh the benefits and risks of early detection with their physicians.

1.1.6 Conservative Management: The Role of Active Surveillance

A consequence of the introduction of the PSA test has been the rise in the ratio of incidence to mortality in recent years\textsuperscript{32}. The dramatic increase in the proportion of low-risk patients and the low rate of prostate cancer mortality in this subgroup has resulted in a number of physicians advocating the conservative strategy of ‘active surveillance’, especially for older men, or those unlikely to tolerate radical treatment well\textsuperscript{33,34,35}. Patients under active surveillance enroll in a program of regular follow-up and evaluation of their disease, with the option to pursue a curative course of action if circumstances warrant. Proponents of active surveillance argue that by delaying or obviating potentially morbid treatment in this demographic, comparable survival rates can be achieved at lower cost and with a higher quality of life.

Those concerned with the potential impact of delayed treatment point to the Swedish experience of ‘watchful waiting’, in which 695 patients presenting with clinically localized prostate cancer were randomized to either observation or radical prostatectomy between 1989 and 1999\textsuperscript{36,37,38,39,40}. By 15-years, the advantages of intervention were clear – a ~25% reduction in the cancer-specific mortality rate. This landmark trial has long been considered a lynchpin in the rationale for definitive management. However, the relevance of these reports to the modern patient diagnosed in the PSA-era is uncertain, the latter often being at substantially lower risk than those comprising the Swedish cohort. Current protocols for active surveillance also include well-defined provisions for advancement to radical therapy. In contrast, the Swedish patients who progressed under watchful waiting were only treated for the ensuing symptoms, which in many cases did not manifest until metastatic disease was evident. In British Columbia, active surveillance is offered to low risk patients, and involves regular PSA tests and DREs, with biopsies every three years. Patients are counseled to begin radical therapy on the basis of a falling PSA doubling time, or when there is significant pathological or clinical stage progression.

Calls to consider active surveillance as a management option are motivated by the potentially severe gastrointestinal and genitourinary morbidity currently associated with all radical treatments. These run the gamut from transient urinary and rectal discomfort to debilitating conditions like impotence, prostatorectal fistula (essentially a hole in the rectal wall), and incontinence requiring permanent catheterization. Although rare, surgical mortality during prostatectomy remains a grim possibility\textsuperscript{41}. Yet the typical patient presenting in the PSA-era is asymptomatic, has a long life expectancy. Moreover, such patients are
increasingly cognizant of the emerging evidence that their cancer may never become life-threatening. It is increasingly falling to such patients to participate in critical decisions about whether to enroll in conservative management, and when to trigger a curative course. The psychosocial impacts of making decisions in this environment are not insignificant. In one study, as many as 26% of men claimed that they would forego a potential survival benefit to avoid the complications of treatment. As the role of active surveillance becomes more prominent, so will the need to ease the anxiety and fear of remorse in low-risk patients for whom the necessity for intervention is unclear. Ameliorating the morbidity of radical management is an important goal in this context.

1.1.7 Radical Management: Treatments with Curative Intent

There are two major options for the radical management of early stage prostate cancer: Radical prostatectomy and radiation therapy ('radiotherapy'). Radical prostatectomy is a surgical procedure indicated for the treatment of local disease, in which the prostate, seminal vesicles, and portions of the vas deferens are excised. The surgery may be performed as an open procedure, or using minimally invasive laparoscopic techniques. The latter involves a much smaller incision through which a flexible probe (the laparoscope) is first inserted to provide illumination, followed by a set of surgical tools that is then operated remotely to perform the excision. In some cases the articulation of these tools is handled by a specialized robotic interface.

Radiotherapy, the other major modality for the radical management of cancer, involves using the cytotoxic properties of ionizing radiation to eliminate tumour cells. At sufficiently high energies, photon interactions with matter result in ionizations - the stripping of electrons from their atoms. These electrons spread outwards from their point of release, imparting energy as they collide with other particles along their tracks. One of the consequences of this electron cascade in tissue is DNA damage. This manifests via direct interactions between the electrons and the DNA bonds, as well as through the production of charged molecules such as the hydroxyl radical which alter the strand structure via chemical reactions. The energy imparted by ionizing radiation is called ‘dose’, and it is measured in Gray [J/kg], an SI unit. Radiation dose is the basic currency of radiotherapy. Analogously to drug treatments, radiation is administered according to a prescribed dose. Prescriptions for radiation therapy are denominated in terms of Gray (Gy) to a particular standardized point, line, or surface in the treatment volume.

The principal aim of radiation therapy is to deliver a sufficient dose to the tumour to control the disease, while simultaneously sparing the patient from the side-effects of radiation to adjacent healthy tissues. The probability of cure is inversely related to the surviving fraction of tumour cells after treatment, which decreases with increasing dose. In this respect, higher doses to the tumour are typically better. However, ionizing radiation damages the DNA of healthy and malignant tissue equally, and radiation cannot be
perfectly confined to the tumour cells. Morbidity results from exceeding the capacity of the healthy ‘normal’ tissue lying in the path of the radiation to recover from damage, and it is this that limits treatment dose. Radiotherapy is about maximizing the therapeutic ratio, the ratio between the likelihood of cure and the likelihood of complications arising from normal tissue toxicity.

Better therapeutic ratios are achieved by manipulating the delivery of the radiation in time and space. Due to intrinsic differences in the radiobiological response of cancer and normal tissue to the rate of dose deposition, there is a general tendency for enhanced relative survival of normal tissue cells if the dose is delivered in small increments, called ‘fractions’, at predetermined intervals. The appropriate fractionation schedule depends on the nature of the cancer being treated. The exposure of the patient to radiation is also carefully planned so as to confine the bulk of the dose to the target region. This allows greater doses to be delivered to the tumour for an equivalent risk of complications. There are two different techniques for radiation delivery in prostate cancer: external beam radiation therapy (EBRT), and brachytherapy.

In EBRT, the radiation source is external to the patient, whose emitted photons are collimated into beams conformed to the treatment target. To avoid excessive surface dose, the treatment geometry typically consists of four to six beams delivered from different orientations so that they intersect in the treatment volume. Planning techniques which spare normal tissue have evolved considerably in recent years. Targets were originally delineated on 2D x-ray images, acquired in the same geometry as the proposed
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treatment beam. This was replaced by a ‘3D-conformal’ paradigm, in which virtual patients are constructed from CT datasets using computers. The 3D dose distributions can then be calculated, viewed, and modified within the virtual environment. Many newer EBRT treatment machines are capable of intensity modulated radiation therapy (IMRT), in which the cross-sectional fluence profile of each beam can be modulated. This translates into significantly sharper dose gradients around the target, sparing nearby sensitive structures. Both standard 3D-conformal EBRT\textsuperscript{46,47} as well as IMRT\textsuperscript{48,49} are routinely used for prostate cancer treatment. The vast majority of centres use photon therapy. However, there has been increasing interest in the use of ionizing proton beams, which theoretically allow even greater confinement of dose to the prostate gland\textsuperscript{34,50,51}.

The second option is brachytherapy, the treatment modality with which this thesis is concerned. As the Greek prefix \textit{brachy} (‘close’) suggests, the defining feature of brachytherapy is the introduction of the radioactive source into or around the treatment site. The principal advantage of brachytherapy is that there is minimal collateral dose deposition to organs outside the target volume. For this reason it is often possible to escalate dose to levels beyond what is tolerable via EBRT. This makes brachytherapy ideal as a monotherapy for low-risk, organ confined prostate cancer, for which there is no need for broad pelvic or nodal irradiation. Brachytherapy may take the form of either temporary or permanent interstitial implantation of radioactivity in the form of small, cylindrical sources.

The vast majority of such treatments for prostate cancer are delivered via permanent implant prostate brachytherapy (PIPB). In this procedure, 80-150 small encapsulated radioactive sources (‘seeds’) are deposited transperineally by 16-30 needles in a planned configuration throughout the prostate gland (see Figure 1.2). These seeds remain in the patient indefinitely, and dose is deposited until the seeds become inert. The most common isotope for low dose rate (LDR) brachytherapy is Iodine-125 (I-125), although Palladium-103 and Cesium-131 are also used. The low photon energies of these species (< 35 keV) are weakly penetrating, and very little radiation is delivered as far as, or beyond, the patient surface. PIPB is typically performed as a single outpatient procedure, under general or spinal anesthetic. PIPB confers outstanding rates of local control in long follow-up, both as a monotherapy\textsuperscript{52,53,54,55,56} as well as in conjunction with EBRT\textsuperscript{57,58,59}.

Temporary, high dose rate (HDR) brachytherapy is also used for prostate treatments. Using a similar transperineal arrangement to PIPB, a set of hollow catheters is implanted into the prostate, and into which an Iridium-192 source is introduced. Modern treatments use a remote after-loading technique in which the source remains in a shielded vault (the ‘after-loader’) during patient setup to minimize exposure to staff. The after-loader is interfaced with each catheter, and during treatment the source, which is attached to a fine cable, is extended remotely. The dwell time of the source at pre-set positions in the catheters is optimized during planning to shape the total dose distribution to the target. HDR brachytherapy can be
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performed as monotherapy, involving 1-4 fractions, or to augment a course of EBRT. HDR brachytherapy for the prostate is a comparatively newer procedure than LDR, but early outcomes series are promising.

The definitive modality for early-stage prostate cancer is controversial, and hampered by the lack of randomized trials, on which the tenets of evidence-based medicine place the greatest emphasis. Unfortunately, the understandable reluctance of patients to be randomized between drastically different treatment procedures has impeded the completion of such trials. The SPIRIT trial, a recent Canadian attempt, closed early due to poor accrual. This was despite concerted attempts to foster informed patient decision making, including consultation in a multidisciplinary environment. However, other efforts, such as the ProtecT (http://www.epi.bris.ac.uk/protect/) and SABRE trials (http://www.controlledtrials.com/ISRCTN88144169) are underway. Currently, the American Urological Association declines to make definitive recommendations for treatment in the absence of randomized evidence. The authors base this decision on a perceived parity in outcomes between the treatment options, and cite the difficulty in integrating disparate series with different technical protocols, heterogeneous cohorts, inconsistent endpoints, and often insufficient follow-up.

The British Columbia’s experience with PIPB has been overwhelmingly positive. Long-term outcomes in a population-based cohort of 1006 consecutive patients have been comparable to the surgical results of top academic centres, and the brachytherapy series of other large institutions. In a set of recently published analyses by BCCA physicians, brachytherapy was found to result in a superior prospect of cure than either EBRT or prostatectomy. The distinguishing feature of these studies was that the cohorts comprising the different arms were either matched by prognostic factors, or, in the case of surgery, those factors were entered into a validated nomogram to predict outcomes for each patient. This included the use and duration of hormone therapy. Although these were not randomized prospective trials, the matched-pair
methodology mitigated the impact of risk heterogeneity between cohorts, one of the principal impediments to an unbiased comparison. The authors acknowledged that the EBRT arm in their study received lower doses than would be prescribed today, but argued that independent data from ultra-high dose IMRT studies suggest that such escalations are unlikely to close the gap in efficacy.

1.2 Prostate Brachytherapy: Technical Background

In this section the technical details of PIPB are introduced. This includes treatment planning, in which the distribution of implanted seeds is decided, as well as brachytherapy-specific dose calculations and the metrics by which the quality of the resulting dose distribution is quantified. The multifarious sources of treatment uncertainty in PIPB and why they necessitate post-implant quality assurance is a major focus. This leads into a discussion of how implant quality is defined and measured, and why this definition should be regarded as institutionally specific. The aim is to introduce the clinical context in which this research was conducted, and to provide the motivation for the proposed improvements to post-implant dosimetry and treatment planning.

1.2.1 Overview

At the BCCA, patients with NCCN low to intermediate risk disease are eligible for PIPB. Contraindications to treatment include exceptionally large glands, unfavorable configuration of the pubic arch, or risk factors for unacceptable treatment morbidity, such as prior urethral resection or other indicators of poor baseline urinary function. Androgen deprivation therapy (ADT) is occasionally given in a neo-adjuvant setting to downsize glands in marginal patients who may otherwise be ineligible.

Before a patient can be implanted, a treatment plan is created to specify the locations in the prostate where seeds are to be placed in order to achieve a desired dose distribution. A modified version of the Seattle preplanning method has been used since the inception of the program in 1998. This method is widely practiced, and has its roots in the late 80’s when Ragde and Blasko first established the technique in North America. Preplanning is so named because the configuration of seeds is determined prior to the operation date (i.e. ‘pre-operative’ planning). In order to do this, patients first attend a clinic where transrectal ultrasound (TRUS) is used to image the prostate gland. The purpose of this is to evaluate whether the gland is suitable for brachytherapy, and if so, to provide the images on which to plan the treatment.

An important aspect of this imaging in a preplanning system is to position the patient as closely to the treatment position as possible, so the images will accurately reflect the configuration of the prostate when the patient returns for implant. The probe is mounted in a cradle which is co-registered to a needle guidance template, through which the needles used to deliver the seeds will later be steered (see Figure 1.3). The cradle has a stepping device that allows the physician to acquire a series of transverse images of
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the prostate gland, from apex to base, at reproducible 5 mm steps. Images are transferred to a workstation by a radiation therapist, where they are used to construct a virtual model of the prostate for treatment planning.

The prostate must be contoured on the TRUS images in order to define a treatment volume. At the BCCA, the therapist first produces an initial delineation of the gland using a semi-automated algorithm\textsuperscript{79,80}. The physician then makes any necessary adjustments to create a clinical target volume (CTV), and adds a treatment margin to produce a planning target volume (PTV). The purpose of the PTV is to increase the treatment target to encompass errors in setup and delivery. In keeping with the Seattle protocol, both the CTV and PTV are rendered laterally symmetric across the mid-sagittal plane.

After the contouring is complete, a medical physicist plans the treatment by deciding where seeds should be implanted. The implantable positions are the intersections between the ultrasound slice depths and the transverse coordinates at which needles pass through the slice. These are defined by the holes in the needle guidance template, which is registered to the cradle. An image of the template is shown at the top left of Figure 1.3. Within the planning software, an image of the grid is projected onto each ultrasound slice to indicate to the physicist where seeds can be placed during planning. In order to avoid damage to the rectum and urethra, only certain template positions can be used.

After the plan is complete, it is sent to a radiopharmacy where the seeds and non-radioactive spacers are loaded in the correct configurations into sterile needles. Although implants can be performed with loose seeds and spacers, most physicians at the BCCA use seed-spacer trains called ‘strands’ that have been embedded in vicryl (polyglactin-910), a bioabsorbable suture (see Figure 1.4). Strands are manufactured by the radiopharmacy from the seed-spacer trains, which are sterilized, loaded into needles, and then delivered to the BCCA.

On the day of the implant, the patient is sedated and placed in the treatment position. The physician maneuvers the TRUS probe so that the live ultrasound images match those of the planning volume study as closely as possible. This simplifies the process of reproducing the patient setup, which is critical to ensuring that the seeds are delivered as planned. The lateral symmetry of the PTV facilitates efficient setup of the patient in the OR, as it is easy to visually confirm, and once achieved, allows the oncologist to focus on calibrating the probe pitch and depth to the planning images. The seeds are then deposited under TRUS and fluoroscopic guidance, according to the treatment plan.
1.2.2 Dose Calculations for Brachytherapy

In order to perform treatment planning and the subsequent implant quality assurance, it is necessary to calculate the dose distribution delivered by the seeds. The AAPM (American Association of Physicists in Medicine) specifies a system of dose calculations for brachytherapy sources in the Task-Group 43 report\(^{81,82}\). This system allows the dose rate to water to be calculated at any point around a seed. Dose rate contributions from all the seeds in the implant are summed at selected grid points to compute the total dose distribution. To compute the total absorbed dose over time, the dose rate is multiplied by the mean life of the isotope being used. Importantly, the TG-43 system does not account for heterogeneity in the medium, or inter-seed attenuation, but it does account for dose anisotropies caused by source materials and design.

A diagram of the model 6711 seed used at the BCCA is illustrated in Figure 1.5. It consists of a titanium capsule with a wall thickness of 0.5 mm, containing a silver rod impregnated with radioactive I-125. Eqn. (1.1) shows the TG-43 2D formalism for the dose rate to water at a point \((r, \theta)\) with respect to the centre of a seed. The 2D formalism is a function of the distance from the measurement point to the centre of the seed, and its polar angle from the seed’s longitudinal axis. However, when the orientation of the seed cannot be determined, the TG-43 1D formalism, shown in Eqn. (1.2), is used. The 1D equation takes the solid-angle weighted average of the dose rate over all possible seed orientations to derive an expression that depends only on distance from the seed.

\[
\dot{D}(r, \theta) = \Lambda \cdot S_k \cdot \frac{G(r, \theta)}{G(r_0, \theta_0)} \cdot g(r) \cdot F(r, \theta) \\
\dot{D}(r) = \Lambda \cdot S_k \cdot \frac{G(r, \theta_0)}{G(r_0, \theta_0)} \cdot g(r) \cdot \phi_{\text{air}}(r) \tag{1.1}
\]

The dose rate equation consists of five factors. The dose rate constant \(\Lambda\) gives the dose rate to water at a reference point per unit air-kerma strength. The reference point is located 1 cm transverse to the long axis of the source. The air-kerma strength \(S_k\) is the rate of energy release in air at a distance \(d\) along the transverse axis of the seed multiplied by \(d^2\). It is measured in units of U (\(\mu\)Gy m\(^2\)/hr), and is proportional to the activity (decays per second) of the seed. The air-kerma strength is specified under the ideal conditions of zero attenuation and scatter in the medium between the source and the measurement point.
The remaining three functions are essentially ratios of dose relative to the reference point. They account for geometric dose fall-off, attenuation and scattering by the absorbing medium (assumed to be water), as well as attenuation, scatter, and other perturbing effects due to the source material and design. The geometry function $G$ describes the fall-off in photon fluence purely due to the geometric relationship between the measurement point and the distribution of activity. TG-43 specifies two models: the point-source model ($G_p$), which expresses the basic inverse-square fall-off from a point source of radiation, and the line-source model ($G_l$), which models the distribution of activity within the source as a one-dimensional line. In this thesis all calculations are performed using a line source model, as it is a more accurate representation of the physical distribution of activity in the seed.

The radial dose function $g$ accounts for the reduction in photon fluence along the transverse axis due to attenuation and scatter in the medium. This is primarily a function of the energy of the radiation. The anisotropy function $F$ accounts for the non-uniformities in dose rate due to source design and self-shielding by the seed casing. Because of fabrication features such as end welds, the photon fluence is non-isotropic.

The effect of this anisotropy is that fluence along the longitudinal axis of the seed is more attenuated than along the transverse axis. Thus, at a given distance, the anisotropy function is at a minimum for angles corresponding to points along the longitudinal axis, and a maximum in the transverse plane.
1.2.3 Dose Prescriptions and Metrics

In EBRT, dose is typically prescribed to a particular consensus point in the patient, such as the centre of the target volume, or in the case of IMRT, to the volume itself. In brachytherapy, however, high dose gradients occur within the treatment volume due to the effects of inverse-square law fall-off at small distances. This makes the dose at any particular point highly sensitive to the precise locations of the sources. Consequently, the dose in prostate brachytherapy is prescribed to the surface of the target volume in terms of a minimum peripheral dose (mPD). The standard mPD for I-125 monotherapy is 145 Gy\textsuperscript{83}.

One of the challenges in modern radiotherapy planning is succinctly expressing the salient features of a complex 3D dose distribution. A widely accepted method is to reduce the dose distribution to a set of cumulative dose-volume histograms (DVHs), one for each of the relevant structures in the irradiated volume. A DVH is plotted as a two-dimensional curve expressing the volume of a structure that receives at least a particular level of dose. An example is shown in Figure 1.6. Two important points on this curve for PIPB are the prostate V100 and D90. The V100 is the volume of a particular structure which exceeds 100% of the mPD, and the D90 is the minimum dose to the hottest 90% of the prostate. These are illustrated in the figure. Similar quantifiers are defined for other dose thresholds, i.e. the V150 and D100. DVH parameters and other values derived from the dose distribution are commonly referred to as dose metrics.

An important concept in radiotherapy is the concept of dose conformity, the extent to which dose is confined to the treatment volume. As discussed previously, dose conformity is critical to achieving a curative dose without significant rates of morbidity. In prostate brachytherapy, dose conformity is usually specified at the prescription level. One method for measuring conformity is the conformity index (CI) which is defined in Eqn. (1.3). It is the ratio of the total volume receiving ≥ 100% of the prescribed dose (Total V100) to the volume of the target receiving the same (Target V100), both measured in absolute
units. This index is constructed so that values greater than unity indicate spillage of the 100% dose volume outside the PTV\textsuperscript{84,85}. In a perfectly conformal implant, the CI is unity, and the Target V100 is equal to the PTV.

\begin{equation}
CI = \frac{\text{Total V100 (cm}^3\text{)}}{\text{Target V100 (cm}^3\text{)}}
\end{equation}

1.2.4 Treatment Planning at the BCCA

The treatment plan for each patient must meet certain standards of dosimetric quality to ensure a high probability of tumour eradication. Recommended dosimetric constraints are set out by professional societies such as the American Brachytherapy Society (ABS)\textsuperscript{83,86} and the AAPM\textsuperscript{87,88}. At the BCCA, planning standards have evolved by building on the basic recommendations. For instance, the geometrical distributions of high dose regions, as well as minimum levels of dose conformity, are specified.

The BCCA uses Oncura® model 6711 seeds containing Iodine-125 (I-125), an isotope with a half-life of 59.4 days that decays by electron capture to produce photons with a mean energy of 29 keV. Seeds are cylindrical, with a physical diameter of 0.8 mm and length of 4.5 mm. The seed air-kerma strength used at the BCCA is 0.42U. In general, the goal is to have the 100% isodose surface encompass the entire PTV, while constraining the V150 and V200 to acceptable ranges, whose numerical values are in Table 1.1. At the base of the prostate, the V100 surface is allowed to dip into the anterior of the target, and a small gap in coverage is permitted at the apex. The V150 is planned with a posterolateral bias, which produces a characteristic horseshoe shaped distribution which can be seen in. Where possible, anteromedial contiguity of the 150% isodose surface is avoided. As the urethra is not visible in the ultrasound images, this precaution aims to spare the expected course of the urethra. It also tends to escalate the dose in the peripheral zone of the prostate where most tumours are believed to originate\textsuperscript{3,4}.

In addition to DVH constraints, implants must meet dose conformity requirements. The maximum tolerances on the deviation between the prescription isodose line and the PTV contour are given in Table 1.2. The tolerance is aspect dependent, and is more flexible on the lateral and anterior surfaces than along the posterior where excessive dose margins may increase the risk of rectal toxicity. Moreover, smooth congruence between the isodose surface and the PTV is preferred, as ragged isodose lines often imply that the underlying seed distribution is unnecessarily scattered. Clipping of the PTV by the isodose surface is avoided.

To create the plan, a medical physicist uses the treatment planning system to display the isodose distribution as seed and needle placements are trialed. The domain of feasible seed positions is defined by the intersection of the needle template grid coordinates with the ultrasound slices. Seeds planned to
different depths at the same template position can be implanted by the same needle, but the addition of even a single seed at a different position requires a dedicated needle. Where possible, the number of needles per plan is minimized for reasons discussed in Section 1.2.7. The main challenges during planning are usually achieving adequate base and apex coverage without either too many needles, or a suboptimal distribution of the high dose regions. The final placement scheme is chosen to produce a dose distribution that deviates from the constraints as little as possible.

In the Seattle method, the PTV and needle configuration is always symmetric across the mid-sagittal plane to facilitate easy registration during patient setup. As much as is possible within the scope of these goals, simple, relatively uniform seed distributions are ideal. Traditional uniform seed distributions are undesirable because these tend to result in maximal doses at the centre of the implant, where the urethra typically passes through the gland. Hybrid loading schemes, such as the one described, that fall between purely uniform and peripheral loading schemes are known as ‘modified peripheral’ or ‘modified uniform’, and typically have better dosimetry.

The seed loading protocol at the BCCA has evolved distinctions from the Seattle method. Needle symmetry is retained, but needle distributions reflect the greater emphasis placed on dose conformity and the desire to shape the V150 to the posterolateral aspect of the gland. To avoid excessive clustering of needles in order to achieve these goals, needle configuration guidelines have been put in place to promote homogeneous seed distributions where possible. As shown in Figure 1.8, no needles are permitted in the central column or in the extreme posteromedial positions to avoid the urethra and rectum. The maximum ranges of seed placements from different aspects of the PTV are listed in Table 1.3. The neighborhood of

Figure 1.7: Coverage of the prostate and PTV (transverse view) in treatment planning. The aim is to have the 100% isodose line encompass the PTV without clipping, although on the most superior slice (base) an anterior defect is acceptable. The 150% isodose is planned in a posterolateral horseshoe to spare the urethra.

The seed loading protocol at the BCCA has evolved distinctions from the Seattle method. Needle symmetry is retained, but needle distributions reflect the greater emphasis placed on dose conformity and the desire to shape the V150 to the posterolateral aspect of the gland. To avoid excessive clustering of needles in order to achieve these goals, needle configuration guidelines have been put in place to promote homogeneous seed distributions where possible. As shown in Figure 1.8, no needles are permitted in the central column or in the extreme posteromedial positions to avoid the urethra and rectum. The maximum ranges of seed placements from different aspects of the PTV are listed in Table 1.3. The neighborhood of
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the PTV, which is considered implantable at the BCCA, includes the seminal vesicles and inferoapical space.

As much as possible, seed and needle configurations are evenly spaced based on the expectation that this reduces the sensitivity of the dose distribution to seed misplacement. Within needles, seeds are typically alternated with spacers so that the distance between seed centres is 1 cm. An occasional exception occurs in central needles, where it may be necessary to reduce the dose by replacing some of the seeds in this alternating pattern with spacers. Such needles are referred to as ‘special loads’. Adjacent seeds are not permitted. The minimum seed spacing in general is \(5\sqrt{2}\) mm, corresponding to in-plane seeds offset by one row and one column of the implantation grid.

1.2.5 Treatment Uncertainties

There are considerable obstacles to accurately delivering the intended dose to the target volume. These arise both from technical challenges in the operating room, as well as from changes in the target volume itself as swelling subsides in the weeks and months subsequent to implant. The latter may also induce unpredictable changes in the positions of the seeds. These effects cause deviations between the planned and delivered dose, which may diminish coverage of the target region and overdose adjacent critical structures, leading to an increased risk of local recurrence and/or morbidity. Identifying and characterizing the impact of treatment uncertainties is critical to improving the oncological outcome and quality-of-life of patients treated with prostate brachytherapy.

In a pre-operative planning (‘preplanning’) paradigm, the patient is ideally in the identical position during both the planning and implant procedures. However, there are practical limitations in the precision with which this can be accomplished. Changes to the patient’s posture may occur due to anesthetization, or variability in the setup of the leg stirrups. There may also be internal differences in anatomical configuration due to bladder or rectal filling, muscle tension, or the effects of hormonal downsizing of the gland itself. The orientation of the ultrasound probe with respect to the anatomy is also important to replicate, as it defines the trajectory of the needles as they are inserted. Any errors in setup will contribute to deviations from the treatment plan, which is part of the rationale for treatment margins.

The difficulty in accurately depositing seeds as planned is the principal source of intraoperative uncertainty in prostate brachytherapy. Frictional forces during insertion result in some deflection of the needle away from its expected trajectory, which introduces errors in the position of intercept. This is compounded by the resultant movement of the gland, and associated deformation of the surrounding soft-tissue. Consequently, it may take repeated insertion attempts by the physician to ensure that the needle tip arrives at the desired location. Moreover, the pose of the seed train is often distorted after the needle is removed.
and the prostate returns to its undistorted state. The phenomenon of lateral splay in anterior needles is one manifestation of this problem, which has been found to decrease mPD by up to 20%\textsuperscript{85,91}. Even if the needle is accurately targeted, seeds may be misplaced during the retraction of the needle. Unintentional clustering and stretching of the seed trains routinely occurs in unstranded (‘loose’) seed implants\textsuperscript{92}. In stranded implants, coverage of the anterosuperior portions of the gland may be compromised if the entire strand is pulled inferiorly during deposition\textsuperscript{93}.
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**Table 1.1: Planning DVH constraints**

<table>
<thead>
<tr>
<th>DVH parameter</th>
<th>Prostate</th>
<th>PTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>V100</td>
<td>≥ 99%</td>
<td>≥ 98%</td>
</tr>
<tr>
<td>V150</td>
<td>56-65%</td>
<td>50-60%</td>
</tr>
<tr>
<td>V200</td>
<td>≤ 22%</td>
<td>≤ 21%</td>
</tr>
</tbody>
</table>

**Table 1.2: Constraints on the 100% isodose margin**

<table>
<thead>
<tr>
<th>PTV Aspect</th>
<th>PTV margin extent (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ant. &amp; Lat.</td>
</tr>
<tr>
<td>Base</td>
<td>7</td>
</tr>
<tr>
<td>Base-0.5cm</td>
<td>7</td>
</tr>
<tr>
<td>Midgland</td>
<td>5</td>
</tr>
<tr>
<td>Largest slice</td>
<td>5</td>
</tr>
<tr>
<td>Apex+0.5cm</td>
<td>5</td>
</tr>
<tr>
<td>Apex</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 1.3: Guidelines for the peripheral placement of seeds**

<table>
<thead>
<tr>
<th>Target Aspect</th>
<th>Placement Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superiorly</td>
<td>Up to the base plane</td>
</tr>
<tr>
<td>Inferiorly</td>
<td>Down to 0.5 cm below the apex plane</td>
</tr>
<tr>
<td>Laterally</td>
<td>Within the PTV, except for the terminal seeds of strands with ≥ 3 seeds, which may be ≤ 3 mm outside the PTV.</td>
</tr>
<tr>
<td>Anteriorly</td>
<td>Within the PTV, except for the terminal seeds of strands ≥ 3 seeds, which may be ≤ 3, ≤ 5, and ≤ 7 mm outside the PTV in the mid-gland, base, and apex respectively.</td>
</tr>
<tr>
<td>Posteriorly</td>
<td>Within the PTV, except for seeds in the base belonging to strands ≥ 4 seeds.</td>
</tr>
</tbody>
</table>
Chapter 1 - Introduction

In one study which compared the planned and post-implant positions of selected seeds, mean discrepancies of approximately 5 mm were noted in the transverse and longitudinal axes of seven patients. Stranded seed implants exhibited less variance in inter-seed spacing and overall length of each seed train as expected. However, seed misplacement magnitudes were comparable. There is some evidence that this may be mitigated by rotation of the needle during insertion to counteract the effect of the needle bevel, which biases the direction of travel. In one phantom study, seed targeting error fell from 2.9 mm to 0.8 mm when a constant rotation was applied to the needle during insertion. However, the tissue trauma that would be incurred by a drilling needle would be significant. Attempts to stabilize the gland with auxiliary needles to reduce motion have not been successful thus far.

The prostate gland swells considerably due to the multiple needle punctures. Literature reports of mean edema magnitude (the maximum percent increase in prostate volume) range from 8% to 65%. This wide range can be attributed to a combination of variability in needle use, patient response, scan timing, and the imaging modalities used to measure volume. Early measurements of edema magnitude were performed by Waterman et al., who used measurements of the seed cloud as surrogates for prostate volume, and reported a mean increase in relative volume of 52%, and an exponential return to baseline with an ‘edema half-life’ of 9.3 days. More recently, Taussky et al. utilized MRI in the post-operative setting to improve gland definition and enable direct volume measurements at one, eight, and thirty days after the procedure. They reported a mean edema magnitude of 31% in their cohort. However, this study relied on TRUS measurements to determine the baseline pre-implant volume. This may have introduced systematic errors as volume measurements depend on the imaging modality due to contouring biases. Consequently, the best estimate of mean edema magnitude is probably 18%, based on a Canadian study in which MRI was used as the sole imaging modality, and the contouring physician was blinded to the chronology of the data. These authors found that edema resolution was better represented by a linear rather than exponential decay, with a period of 28 days.

In addition to changes in volume, the fixity of seeds in the weeks following implant is also variable. Seed loss is quite common, and inevitably diminishes the dose distribution. Seeds may embolize through the venous plexus, which surrounds the prostate gland, to the lung, or be lost through ejaculation or transurethral routes. Pulmonary embolism, which is a more considerable risk when there are extensive extraprostatic seeds, was the primary reason that stranded seeds were introduced at the BCCA. Seeds may also exhibit smaller, local displacements. Some investigators have reported the tendency for strands to shift inferiorly during the first month, an effect they associated with the resolution of edema. Specifically, they suggested that strands may be anchored in the levator ani, a muscle which sits inferiorly to the prostate. Subsequent movement of the prostate relative to this muscle results in the strands being extracted from the gland. The frequency of this effect is somewhat controversial, as other
institutions, including the BCCA, have not found evidence that this occurs systematically\textsuperscript{106,107}. Conversely, loose seeds are commonly assumed to remain fixed relative to the prostate during the resolution of edema\textsuperscript{98,108,109}.

1.2.6 Post-implant Analysis

The significance of intraoperative uncertainty in PIPB has led the ABS and AAPM to recommend post-implant analysis for every patient\textsuperscript{87,110}. The standard post-implant protocol is to acquire a pelvic CT scan on which organs are contoured and the seed positions are determined in order to reconstruct the dose. The 2009 AAPM TG-137 report\textsuperscript{88} recommends, as primary parameters, reporting the prostate D90, V100, and V150, along with the rectal D2cc and urethral D10. The main purpose of post-implant analysis is to verify that the treatment goals have been achieved, and provide feedback to the oncologist to aid technique refinement.

Routine post-implant analysis is a critical component of prostate brachytherapy quality assurance. If the dose distribution is identified as being deficient, the patient may be recalled for an implant revision in which additional seeds are added to augment the dose\textsuperscript{111}. Although this is rare, failing to adequately monitor post-implant doses may have severe consequences. At the Philadelphia Veterans’ Affairs Medical Center in 2009, the treatment of 62 patients was compromised because poor implants went unnoticed\textsuperscript{112}.

One challenge in post-implant analysis is accounting for the effects of edema, as the prostate and seed configuration seen on the CT scan may still be evolving as swelling subsides. As a consequence of this uncertainty, the optimal evaluation time is somewhat controversial. At the BCCA, post-implant analysis is ‘day-0’, which means that the patient is imaged immediately after recovery. Day-0 analysis has the advantages of patient convenience and the timely identification of poor implants. However, it may be a premature estimate of the final quality of the treatment. For I-125, approximately 70% of the dose remains to be delivered after edema has resolved. Thus, many centres delay post-implant analysis until edema subsides to ensure a more accurate picture of treatment quality.

The dosimetric impact of edema was first investigated in a pair of influential studies\textsuperscript{113,114}, based on the model of prostate edema proposed by Waterman et al\textsuperscript{98}. Using this model, the relative error of the post-implant dose distribution with respect to the plan was computed for different values of edema magnitude and half-life. The authors concluded that the optimal time for analysis was 42 days, a recommendation adopted by the AAPM TG-137 report\textsuperscript{88}. In practice the delay is usually closer to 30 days (‘day-30’ dosimetry). The aforementioned studies were predicated on the assumption that seeds move in synchrony with the prostate tissue, and therefore that changes in the positions of seeds correspond to equivalent deformations in the underlying tissue. However, this hypothesis has not yet been tested in loose seed implants, to say nothing of stranded techniques that often include substantial periprostatic implantation.
Chapter 1 - Introduction

The subject of much of this thesis is to investigate, and in some cases address, current limitations in the accuracy of post-implant dosimetry. These contributions are important not only in order to develop the capacity to compute post-implant dosimetry of implants with seeds of different activities, but because post-implant dose metrics are the basis for implant quality. The accuracy of post-implant analysis is crucial, as it underpins any evidence-based approach to linking dosimetric and clinical endpoints. For reasons discussed, this is particularly salient in the context of early-stage prostate cancer, when a clear picture of clinical efficacy substantially lags the provision of treatment in a field of constant technical innovation.

1.2.7 Implant Quality and Outcomes

At the BCCA, implants are broadly categorized for the purposes of quality assurance as excellent, good, or suboptimal, on the basis of the prostate D90 and V100. ‘Excellent’ implants have 180Gy > D90 > 144Gy and V100 > 90%. ‘Good’ implants have 130Gy < D90 < 144Gy or 180Gy < D90 < 200Gy and V100 > 85%. Implants outside these thresholds are considered to be ‘suboptimal’. Although urethral and rectal doses are planned to <150% and <100% of mPD respectively, no explicit quality thresholds currently exist for these structures in the post-implant setting.

These strata are loosely based on the work of Stock et al. at Mount Sinai Hospital in New York, who first demonstrated a relationship between post-implant dose metrics and BDFS. They followed 134 patients treated at their clinic, and reported that D90 values of ≥140 were associated with 5-year BDFS rates of 92%, as compared to 68% for those patients with D90<140. This was supported by a large multicenter study which showed a divergence in the BDFS between patients who did and did not meet this cut point. More recent data from their institution suggests that escalating D90 even higher (i.e. >180Gy) can improve outcomes, and is reasonably well tolerated by patients, if careful attention is paid to limiting dose to the urethra and rectum.

As a result of these publications, there is a trend towards dose escalation. However, the specificity of a particular set of dose thresholds to biochemical survival in the wider context of the brachytherapy community is controversial. Effective thresholds may depend on treatment techniques, which differ between institutions. At the BCCA, there is no evidence that exceeding a D90 threshold correlates with treatment success, despite the fact that survival rates for brachytherapy patients in the province rival those of Sinai and other institutions. A similar lack of dose response is evident in other brachytherapy series as well.

One reason for this may be that consistent treatment success is more dependent on achieving adequate peripheral coverage than a high D90. From this perspective, it is the wide dose margins that occur as a
side-effect of a high D90 that are therapeutic, especially in Centres which do not implant the periprostatic region. The importance of treating extraprostatic disease extension, which is known to be present even in low risk disease, may be why these institutions see a clear benefit to dose escalation\textsuperscript{122,123}. Increasing D90 in programs where extraprostatic dose margins already exist by design may simply be an invitation to greater toxicity\textsuperscript{124,125,126,127,128,129}. Disparities of this sort underscore the need for a technique-conscious approach to dosimetric goal-setting, articulated by, and validated through, a comprehensive quality assurance program.

One of the weaknesses of parameters such as prostate D90 and V100 is that they do not identify which regions have been undertreated, and efficacy may depend on where these lapses occur. To address this, the BCCA pioneered quadrant dosimetry, a form of sector analysis in which dose metrics were evaluated in four sub-regions of the prostate\textsuperscript{93}. Quadrant dosimetry is performed by dividing the prostate along the mid-transverse and mid-coronal planes into four quadrants: the anterior-superior (ASQ), anterior-inferior (AIQ), posterior-superior (PSQ), and posterior-inferior (PIQ). The V100, V150 and D90 were evaluated in each quadrant. The data showed that dosimetric deficiencies were almost entirely confined to the ASQ, which was the only quadrant in which D90 was less than 144Gy and V100 was less than 90%. Thus, whole prostate measures of quality at the BCCA, particularly D90, tend to be driven by coverage of the ASQ\textsuperscript{130}.

Covering the ASQ consistently is a challenge. There is little implantable tissue superior to the gland in this region, as the bladder sits immediately adjacent. Implanted the bladder-prostate interface is difficult, and if the bladder is perforated as the physician tries to place seeds in the bladder wall, those seeds are at greater risk of being voided in the urine. Recognizing this, oncologists often implant strands shy of their planned depth in this region. The caudal ends of these strands then protrude excessively from the apex, leading to higher doses to the membranous urethra and penile bulb, inadvertently elevating the risk of stricture and impotence. Moreover, such strands may also be at greater risk of being anchored in the inferoprostatic musculature, with the concomitant risk of further inferior migration by extraction. It should also be noted that that the measurement of ASQ dose is quite sensitive to contouring uncertainty. The prostate is difficult to distinguish from the bladder neck on CT\textsuperscript{131}, which can result in overestimating the extent of the prostate during post-implant analysis. However, given the multiple factors involved, it is likely that such overestimations simply exaggerate an existing problem.

Thankfully, low ASQ doses have not been associated with biochemical failure at the BCCA\textsuperscript{130}. This has, in the past, been attributed to the lower expected tumour burden in this region\textsuperscript{3,4}. However, new evidence from saturation biopsy studies suggests that cancer foci in the anterior base may be more common than previously thought\textsuperscript{132}, especially in the higher risk patients that have been recently deemed eligible to receive brachytherapy. Sustaining higher doses in the ASQ may benefit these patients if this can be done without increasing the risk of urinary toxicity associated with dose to the bladder neck\textsuperscript{127,129}.
This risk of elevating urinary toxicity is the other edge of the dose escalation sword. Relative to EBRT, brachytherapy typically has greater urinary morbidity, notably in the onset of late effects. Recall that the modern prostate cancer patient is far more likely to present younger, with asymptomatic PSA-detected disease, and decades of life expectancy. Post-treatment quality-of-life is therefore a vital consideration in the treatment of these patients. The incidence of serious urinary toxicities, considered herein to be those greater than Grade 3 on the Radiation Therapy Oncology Group (RTOG, www.rtog.org) scale, is not inconsiderable. This grade includes greater than hourly frequency, with pain and spasms that demand narcotics, and possible hematuria. Of particular concern is obstruction and the potential development of acute urinary retention (AUR), a severe event that has been found to significantly predict poor longer term quality-of-life outcomes.

In a cohort of 712 consecutive patients, Keyes et al. at the BCCA reported AUR rates of 9%, with 16.2% of patients reporting Grade≥3 toxicity. These rates are improving with experience – a more recent subset of 200 patients had AUR rates of only 6.3%. Late Grade 3 toxicity, meaning that the onset of symptoms occurs after a year, was 6.5%.

The most popular prescription to programs aiming to improve dosimetric results and reduce treatment sequelae has been to adopt interactive planning, with ‘dynamic’ (real-time) dosimetry. In contrast to preplanning, interactive plans are created on intraoperatively acquired images and updated in response to the implanted dose distribution. Centres that migrate to intraoperative planning typically report an improvement in dosimetric endpoints.

The current protocols for interactive planning are built upon treatment techniques quite dissimilar to that of the BCCA, featuring loose seeds of higher activities which are strictly confined to the gland. Implementing these methods would require dramatic and expensive changes in practice at the BCCA. Given the local wealth of experience with preplanning, and its documented successes, it is unclear whether such changes would benefit British Columbians. Moreover, on closer examination, the dosimetric benefits accrued by émigrés to intraoperative planning leave wide room for interpretation. In all reports, interactive planning is sequentially introduced, which ignores the tendency for dosimetry and outcomes to improve with experience. In one influential study, significant differences existed between the preplanning and intraoperative planning arms unrelated to the technique, such as increases in total activity of 25% in the intraoperative arm. In another study, post-implant mean D90 and V100 after implementing intraoperative planning improved from 120.5 Gy and 76.2% to 136.5 Gy and 85.9% respectively, results that still fall short of what is routinely achieved at the BCCA without dosimetric feedback. In fairness, that study is a decade old, and may be unrepresentative of their current outcomes.
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A more recent Canadian study described the initiation of intraoperative PIPB at the Tom Baker clinic in Calgary, making the case that intraoperative methods obviated the learning curve. The reported mean post-implant to planned D90 ratio was 0.79 in the inexperienced group, in comparison to 0.85 at the more experienced Hôtel-Dieu de Québec. At the BCCA, this ratio is already ~0.85. Given the differences in protocols, this experience suggests that a transition to intraoperative planning would result in a temporary degradation in dosimetry followed by a return to the status quo.

With respect to clinical endpoints, the BCCA data is broadly comparable to institutions that plan intraoperatively. The 7-year actuarial BDFS rate at the BCCA is 94%, as compared to 5-year BDFS rates of 96% and 97% at Memorial Sloan Kettering Cancer Centre (MSKCC) and Mount Sinai respectively, institutions which perform intraoperative planning exclusively. Although there are the inevitable confounders between the series with respect to cohort composition, follow-up, and use of adjuvant hormones, these factors do not grossly favour the BCCA cohort. With respect to urinary toxicity, MSKCC reported a reduction in mean urethral dose from 263 Gy to 140 Gy after introduction of intraoperative planning, which was associated with AUR rates of 8% and late Grade 3 toxicity rates of 4%. The Mount Sinai group reported AUR rates of 12.4%. Baseline functional scores, which are important prognostic factors, were similar between these groups and the BCCA, whose whole-cohort rate of AUR was 9%. The intraoperative methodology advocated by these institutions does not appear to confer a distinct advantage in either BDFS or AUR rates.

Intraoperative protocols also preclude many of the logistic and cost efficiencies of preplanning. Seed loading would have to be performed on-site in the operating room, and it is unlikely that the pre-implant ultrasound study could be entirely averted if strands continue to be used. A dedicated physicist must be present in the operating room to conduct treatment planning, which presents a significant staffing obstacle at a high-volume treatment centre. To warrant the resources necessary to shift the burden of planning into the operating room, the evidence of a benefit should be overwhelming. Yet the differences in BDFS and rates of toxicity do not speak to an advantage pronounced enough to abandon the current methodology. From a Canadian perspective, given the resource differential, a compelling case could actually be made for the reverse.

This is not to say that real-time plan adaptation is undesirable, only that an intraoperative protocol that requires significant changes to how the BCCA plans seed distributions or loads needles is unlikely to take root. Concurrent research at the University of British Columbia is underway to develop on-demand intraoperative dosimetry. This will be invaluable for the guidance of the small number (≤5) of additional seeds that are occasionally used to augment coverage after the planned seeds have been implanted. This process is currently informed only by perceived gaps in the seed distribution with respect to the plan. One promising approach has been pioneered by researchers in Guildford, who have designed a hybrid strand-
Chapter 1 - Introduction

based intraoperative methodology in which peripherally implanted strands are bolstered with intraoperatively planned loose seeds at the base and apex\textsuperscript{147}.

Within the context of the current BCCA treatment protocol, there is still potential to improve dosimetry and reduce toxicity. One of the significant factors predicting long term catheterization after AUR at the BCCA was the number of needles used in treatment\textsuperscript{134}. This was also implicated in the time taken for patients in the cohort mentioned above to return to baseline function. In a large series at the Utrecht centre in Holland, in which half of the patients were treated with a preplanned stranded technique, only prostate volume and pre-treatment urinary function, which were also factors at the BCCA, were significant predictors for the onset of AUR. This may be because their higher implant activity (0.51U vs. 0.42U) reduces the number of needles, and subsequent trauma, below the threshold to see a needle-dependent effect. In general, the association with number of needles is consistent in the literature. Centres which use higher activity seeds and fewer needles tend to report lower rates (8.0-12.7%) of AUR than those which use lower activity seeds and more needles (10.9-19.7%)\textsuperscript{135,126}. Anecdotal experience of a reduction in acute toxicity after the BCCA switched to seeds delivered through narrower 20 gauge needles suggests that, at least below some threshold, trauma rather than dose becomes the critical factor. This is further supported by a study that found AUR in 11.5% of patients receiving transperineal biopsies in which no radiation was implanted\textsuperscript{148}.

Reducing needle counts through the use of higher activity seeds within the program has been controversial. Low activity seeds allow finer control of the dose distribution, which is important to meet the stringent conformity requirements and facilitate the shaping of the V150, as described in Section 1.2.4. Seed loss in high activity implants also has a higher proportional impact on the total dose distribution. There have also been concerns about the risk of rectal fistulae if high activity seeds are misplaced near the rectal wall.

In this thesis the proposed solution to mitigate low ASQ doses and reduce needle counts is to plan implants with seeds of different strengths. Such variable strength implants could use stronger seeds in locations where the consequences of misplacement are low, while retaining weaker seeds near the rectal wall and periurethral regions. The use of stronger seeds at the tips of the anterior needles may allow those seeds to be planned further from the bladder wall while still covering the base. Such modifications in planning may reduce the risk of deteriorations in coverage that result from strand migration into the bladder, a phenomenon which is investigated in this thesis. Similar modulations in activity would reduce the need for strands to extend into the levator ani to provide coverage to the apex, potentially suppressing the risk of inferior strand migration.

The concept of implanting sources of variable strengths is not new. The classic Patterson-Parker scheme for generating uniform dose distributions in a volume called for greater activities at the periphery of the
implant\textsuperscript{140}. However, modern PIPB practice demands post-implant analysis, in which seeds are indistinguishable from each other in terms of their activity. This difficulty is surmounted by the plan reconstruction technique, to which this thesis turns in the next chapter.

1.3 Thesis Objectives

This thesis comprises a body of research aimed at expanding the capability and improving the accuracy of post-implant dosimetric calculations and procedures in low dose rate prostate brachytherapy. A number of advances are made in this respect. An important contribution of this thesis is a technique referred to as plan reconstruction, which automatically determines the correspondence between seeds found in the post-implant CT, and the preplan. The algorithm underlying the method is described in Chapter 2, where the accuracy of the derived correspondence is compared to a previously published method in 70 implants. The capability to compute a correspondence was an indispensable component of the studies that comprise the remaining chapters, and an accurate automated method is a prerequisite to a feasible clinical implementation of mixed-activity treatments.

One of the collateral benefits of plan reconstruction is that the seeds which comprise individual strands can be grouped to identify the track of each needle. In Chapter 3, a novel method for determining seed orientations is presented, based on computing the tangent of spline curves fit to the positions of the seeds in each strand. By using the tangents to approximate the seed orientations, the current standard 1D dose calculation used for dosimetry calculations can be replaced with the more accurate 2D formalism. The resulting impact on post-implant dose metrics was investigated in 30 patients. The results showed that the 2D dose calculations did not have a substantial impact on low-activity dose distributions with large numbers of seeds. However, in a future mixed-activity protocol in which fewer seeds are responsible for covering the base and apex, the effects may be more pronounced.

The variability of stranded seed fixity during the resolution of edema is investigated in Chapter 4. Using the correspondences generated by plan reconstruction at two time points, individual seed displacements were tracked during the first month post-implant in 28 patients. These displacements were then compared to those predicted by previously published edema models. In addition, plan reconstruction made it possible to identify the specific strands and anatomical regions in which seeds are most at risk of post-implant migration. These findings provide the evidentiary rationale for reducing the proximity of strands to the bladder wall and beyond the apex, which mixed-activity methodology may accomplish in the future.

In Chapter 5, the dosimetric robustness of treatments planned using high and mixed-activity implants are presented. Using standard low activity (0.42U) clinical cases as a control, three experimental (high or mixed-activity) plans were generated for each of 28 patients. The first plan used only 0.6U seeds, whereas
the second two used a mix of 0.42U, 0.6U, and 0.9U seeds. Each experimental plan used a subset of the seed positions of the clinical plan, and was required to satisfy the clinical dosimetric constraints described in Section 1.2.4. The post-implant dosimetry of these plans was simulated by mapping the activities of the seeds in these plans onto the post-implant CT scans, using the correspondence derived by plan reconstruction. The inclusion of the high activity plan was to establish whether comparable dosimetry was possible using this less complicated methodology. This chapter represents the first study of mixed-activity PIPB that has used post-implant dose metrics as an endpoint, thereby providing a clinically realistic depiction of the dosimetric results.
Chapter 2 – Plan Reconstruction

2 Plan Reconstruction

2.1 Introduction

At most institutions, post-implant analysis involves three steps: the delineation of structures of interest, the localization of seeds, and the computation and evaluation of dosimetric endpoints. CT-based analysis is the current standard for post-implant dosimetry. For implants which are composed of single species of seeds with a nominally uniform activity, the correspondence between the planned and the segmented seed cloud is unnecessary for the reconstruction of the dose distribution. Thus, seed identification has historically consisted only of localizing the seeds as they appear on the post-implant CT scan, without reference to the pre-implant plan. Computing this correspondence, referred to herein as *plan reconstruction*, enables many improvements to prostate brachytherapy practice from the perspective of both implant quality assurance as well as planning.

Plan reconstruction has been performed manually to identify needles and seeds to generate actuarial estimates of misplacement and migration\(^{92,94,149,150}\). The more sophisticated of the studies model misplacement taking into account needle delivery effects, such as the clustering of loose seeds near the point of implantation. Another important factor affecting dosimetric outcomes is the anatomical site of delivery, and the associated risk of migration from that site. Distant migration via transurethral routes or pulmonary embolization is well documented\(^{85,102}\). Needle splay, which may account for 10-20% reductions in minimum target dose\(^{91}\) is more likely to affect anterolateral needles than their posterior counterparts\(^{93}\). Plan reconstruction not only assists in the characterizations of these errors, but offers a tool to quantitatively address issues such as the suggestion that stranded seeds are prone to craniocaudal migration during the resolution of edema\(^{103,105}\). A thorough investigation of these phenomena requires strand correspondences at each time interval, so that any systematic movement can be tracked.

The first automatic algorithm for plan reconstruction used a simulated annealing strategy to find a correspondence that minimized the weighted sum of the distances between the expected and final positions of each seed\(^{151}\). In this method, seed positions in ultrasound and CT were parameterized relative to their respective centre-of-seed-mass to address the lack of a common coordinate system. In a series of reconstructions on 58 preplans on which a seed migration model was applied to create a synthetic post-implant distribution, it was found that accurate identification depended primarily on seed density. For medium seed densities of 1.69 cm\(^{-3}\), 89% of seeds were accurately identified, falling to 80% at densities of 2.25 cm\(^{-3}\).

In this paper, a new method for automatic plan reconstruction is presented which incorporates inter-seed relationships to achieve a more robust representation of the treatment plan. With a model that includes the relative positions of planned seeds, matching penalties can be levied not only in terms of the expected
position, but also for correspondences that result in incoherent needle paths. In principle, any implant with a planned spacing can be characterized by that spacing. However, this methodology was principally developed for the reconstruction of stranded implants, in which the constrained spacing is a highly specific test of the correct assignment of seeds to strands.

This chapter is organized as follows. First, the features of BCCA treatment plans are described to provide some context for the types of seed distributions on which plan reconstruction is being performed. Second, the creation of manual reconstructions, which form the set of reference correspondences to which the automatic algorithm was compared, is described. The description of the algorithm itself begins with how coarse registration of the preplan and postplan seed clouds is performed, followed by an introduction to the error functions which comprise the measure by which putative correspondences are evaluated. Plan reconstruction is then formalized as finding the set of correspondences which optimize this measure, and the remainder of the methods section is devoted to explaining how to effectively treat the optimization problem. In the results, the performance of the algorithm, which is referred to henceforth as the $S_{reconstruction}$ algorithm, and the results of its application to the test cases are presented, focusing on the improvements to reconstruction accuracy in relationship to an implementation of a simpler algorithm which does not incorporate inter-seed relationships during matching.

2.2 Methods

2.2.1 Planning Guidelines

For this study, the pre- and post-implant seed coordinates (referred to hereafter as the ‘preplan’ and ‘postplan’) of 70 implants were exported from the VariSeed (Varian Medical, Palo Alto, CA) planning software to form a test set for reconstruction. As such, the data represents a non-consecutive retrospective cohort of patients implanted during 2008 and 2009. Selection was not directly informed by any pre- or post-implant dosimetric quality indices, by prostate size, possibility of pubic arch interference or by the experience of the physician who performed the implant. A small number of cases (5) were an exception to this and were chosen to round out the range of seed/needle counts in the dataset. Cases were non-consecutive because of the need to exclude those for which there were undocumented changes to the plan on the day of the procedure, for example to address differences in the configuration of the patient anatomy due to anesthesia. This was to ensure that the treatment plan was an accurate model of the implant that was actually attempted. The resulting dataset covers a representative range of implant seed numbers, (mean 109, range 70 to 146) and ultrasound preplan PTV seed densities (mean density = 2.0 seeds/cm$^3$).
range 1.6 to 2.6). Automatic seed segmentation was performed prior to reconstruction, using a combination of intensity-thresholding, morphological filtering, and redundancy checking to automatically locate the centroid of each seed.

### 2.2.2 Manual Plan Reconstruction

To visualize reconstructed plans, and correct any errors in the automatic reconstruction process, a graphical user interface for plan reconstruction was created to allow the user to assign seeds to strands. In the 3D display, seeds that are identified to strands are connected by lines to visualize the trajectory of the putative strand. An example of a reconstructed clinical case is shown in Figure 2.1. The expected relative positions of strands, the seed count and spacing within the strand, and the similarity in curvature with neighboring strands are used to deduce the reconstruction. All test cases in this study were first reconstructed manually, and these reconstructions were considered the reference standard for the automatic algorithm. Due to the use of stranded sources, there is far greater certainty that the manual reconstruction is correct than appears to be the case with loose seeds. Nonetheless, the manual reconstructions were all verified independently by two to three experienced brachytherapy physicists who reached a consensus on the reconstruction in each case.
2.2.3 Chapter Overview

The basic idea behind automatic plan reconstruction is to design an objective function of the correspondence between the preplan and postplan which rewards certain expected properties of an accurate reconstruction, and then find the correspondences which maximize it using optimization techniques. To do this, a quantitative measure to assess the similarity between a pair of seeds in the preplan and a pair of seeds in the postplan is developed called the Similarity function. The Similarity is based on three criteria: the relative positions of the seeds, the differences in the angles the line that connects them makes with a reference direction, and the differences in their spacing. In order to present a concise form of the Similarity function, these criteria will be developed and discussed individually before the function is introduced.

Although the formalism of plan reconstruction is general, for clarity the illustrations in this paper will use a three-strand case as an example. This is introduced in Figure 2.2, which shows two possible reconstructions of the three strands, defined by their unique correspondence matrices. The strand connections that the correspondence implies in the postplan are illustrated on the right of the figure. Looking at the figure, the reconstruction on the top is clearly correct; the strands are close to their planned positions, and have approximately the correct spacing. In contrast, in the poor reconstruction below, strands are not at their expected positions, and seed spacing is either inconsistent or, in the case of the four-seed strand, entirely incoherent.

The $S$-reconstruction algorithm has three steps. The first step is to coarsely register the preplan and postplan seed clouds to bring them into approximate alignment. This also addresses differences in the coordinate systems from which they are clinically acquired. In the second step, a sub-problem is solved which yields likely strand paths through the postplan seed cloud. In the third step, these strand paths are used to inform a matching algorithm which finds the optimal correspondence. These steps are summarized in Figure 2.3 with respect to the three-strand example.
Chapter 2 – Plan Reconstruction

Figure 2.2: Plan reconstruction is the process of finding the best correspondence between the preplan and postplan.

(i) The preplan and postplan seed clouds. An arbitrary numbering scheme is used here to reference each seed. Strand connections are known in the preplan. The goal of plan reconstruction is to find the correct correspondence.

(ii) On the left, two correspondence matrices describe different reconstructions of the seed clouds on the right. The preplan numbers above the postplan seeds in the diagrams indicate the correspondence.

2.2.4 Terminology and Notation

In developing a general formalism for plan reconstruction, this chapter considers a treatment plan of \( N \) seeds loaded into \( K \) strands. The variables \( a \) and \( b \) are used to index seeds in the preplan, and \( i \) and \( j \) are used for the postplan. Strands in the preplan will be indexed by \( k \), and in the postplan by \( \kappa \). Positions of seeds and strands are denoted by the vector \( \mathbf{r} = (x, y, z) \in \mathbb{R}^3 \), so that, for example, the position of the \( a^{th} \) seed is \( \mathbf{r}_a = (x_a, y_a, z_a) \). For compactness, the vector difference between seed positions \( \mathbf{r}_i - \mathbf{r}_a \) is abbreviated \( \mathbf{r}_{ia} \).

At the BCCA, a rectilinear template is used to guide the needles, which are all planned parallel to the \( z \) axis of the registered frame, defined by the long axis of the ultrasound probe. The angle made by the line segment connecting seeds \( i \) and \( j \) with respect to the line parallel to the \( z \)-axis that passes through \( \mathbf{r}_i \) is denoted \( \alpha_{ij} \). These definitions are illustrated in Figure 2.4. With respect to the patient \( x \), \( y \), and \( z \) are the lateral, anterior-posterior, and inferior-superior axes respectively, in the ultrasound frame of reference.
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The binary correspondence matrix used to represent a one-to-one correspondence between the pre- and postplan seeds (as in Figure 2.2) is denoted \( M \in \mathbb{R}^{N \times N} \). \( N \) elements of \( M \) are one, and they correspond to the intersection of the \( a \)\(^{th} \) row (preplan seeds) with the \( i \)\(^{th} \) column (postplan seeds). The remaining entries of \( M \) are zero.

The strand structure of a treatment preplan is formalized by a binary \textit{preplan strand connectivity matrix} \( E^{\text{pre}} \in \mathbb{R}^{N \times N} \) whose element \( e_{ij}^{\text{pre}} \in E^{\text{pre}} \) is one if and only if seed \( b \) is in the same strand as \( a \), and zero otherwise. A similar \textit{postplan strand connectivity confidence matrix} \( E^{\text{post}} \) is defined for the postplan.
whose element $c_{ij}^{\text{post}} \in E^{\text{post}}$ is greater than or equal to one if seeds $i$ and $j$ are potentially connected, and zero otherwise. Values larger than one reflect a greater degree of confidence that the connection is correct.

The distance at which seeds in the preplan are spaced is always a multiple of 5 mm for the strands used in this study. These discrete spacings are indexed by $l \in 1...L$, where $L$ is maximum spacing index in the plan: the number of 5 mm intervals between terminal seeds in the longest strand. Each index is associated with distance $d_l = 5l$ mm (see Figure 2.4). Note that given $a$ and $b$, the spacing $l$ is implicit, since the spacing can be computed from the difference in position of the seeds ($d_l = \left\| \mathbf{r}_{ab} \right\|$).

Many of the algorithms used in this paper are canonically described in graph-theoretic terms\textsuperscript{152}, and the steps of the plan reconstruction process we propose are most intuitively visualized using graphs, in which an object is abstracted into a set of vertices, which represent features or other attributes, and edges, which connect the vertices and describe a relationship between them. Formally, a graph $G = (V,E)$ is composed of vertices $v_1, v_2 \in V$, and edges $(v_1, v_2) \in E$. In the graphs that are introduced subsequently, vertices always represent seeds and so for simplicity ‘seed vertex’ and ‘seed’ are used interchangeably.

### 2.2.5 Step 1: Coarse Registration of the Postplan to the Preplan

Since planning is performed on ultrasound images and the postplan localized on CT, the origin and rotation of the imported seed clouds are different. Because the reconstruction algorithm is based on a comparison of the relative positions and orientations of the seeds comprising the preplan and postplan, it is expedient to begin by coarsely registering the two together to address the differences in their coordinate systems. This (rigid) registration is accomplished in the standard manner of iteratively estimating a correspondence, and computing a translation and rotation that minimizes the distance between seeds in that correspondence, as is done by the ubiquitous iterative closest point (ICP) registration method\textsuperscript{153}.

In ICP, the correspondence is estimated using a nearest-neighbor criterion, but in this study, a more accurate, application specific criterion than nearest-neighbor is developed, which is introduced in the next section. The result of the registration is that the centers of seed mass (the average position of the seeds) in each cloud are coincident, and the trajectories of strands within the postplan are approximately aligned parallel to the ultrasound $z$-axis.

#### Positional correspondence error

The positional correspondence error is the first of three error terms which are used to quantify the similarity between a seed in the preplan and postplan. This error is a weighted distance between the pre- and postplan seed in the registered frame. One way to interpret the preplan is as the set of expected positions of seeds in
the postplan. In a perfectly executed implant in a rigid phantom, with high-precision post-implant imaging, all postplan seeds would be at their expected positions, and plan reconstruction would be trivial. In a realistic clinical setting, the combined effects of prostate edema, seed misplacement, probe distortion of the gland, variations in patient position between imaging modalities, and finite segmentation precision routinely cause the postplan seeds to be substantially offset from their expected positions. Nonetheless, it is assumed that the likelihood of correspondence between any seeds $a$ and $i$ decreases as the difference in their positions increase, and the positional correspondence error reflects this.

The variance in the distribution of the displacement of postplan seeds from their expected position is consistently different along each axis due to the geometry of the implantation\textsuperscript{94,96,154} and the relatively lower axial precision of the CT scanner. In addition, the accurate placement of a seed in the transverse plane is easier to achieve than along the needle track. As a result, the error term is constructed with axis specific weightings, so that the apparent error of a correspondence for which the difference vector is principally along an axis of high variance is lower than it would be if the vector were along an axis of low variance. The weights were derived from the standard deviations in the distance-to-correspondence in each axis of seeds in the first 50 manual reconstructions. These (sample) standard deviations are denoted $sd^x$, $sd^y$, and $sd^z$. The value of these, and all subsequent standard deviations measured on the data are available in Table 2.1.

Using these, the positional correspondence error $\Delta_{ai}^{pos}$ is defined:

$$
\Delta_{ai}^{pos} = \sqrt{\left(\frac{x_a - x_i}{sd^x}\right)^2 + \left(\frac{y_a - y_i}{sd^y}\right)^2 + \left(\frac{z_a - z_i}{sd^z}\right)^2}
$$

(2.1)

With some differences in how each term is weighted, the sum of $\Delta_{ai}^{pos}$ over the correspondence is equivalent to the ‘energy’ metric of Archambault \textit{et al.}\textsuperscript{151}, which those investigators minimized to perform reconstructions in their study. As this type of reconstruction essentially minimizes the summed distance between corresponding seeds, such reconstructions will be referred to as ‘Minimum Distance’ (MD) reconstructions. With respect to the notation used in this study, an MD reconstruction is a correspondence which satisfies the following (‘argmin’ being short for ‘the argument that minimizes’):

$$
M^{MD} = \arg\min_{a} \sum_{i}^{N} m_{ai} \Delta_{ai}^{pos}
$$

(2.2)

Eqn. (2.2) is an example of a linear assignment problem. Such problems are often encountered in operations research when finding the optimal one-to-one allocation of group of people to a set of tasks, given that the proficiency of each person at each task is quantified. An intuitive application of this might be the problem of optimally matching conference papers to reviewers with different areas of interest and
degrees of expertise therein\textsuperscript{155}. In a more closely related example, investigators have used linear assignment methodology to find correspondences between seeds in planar fluoroscopic images of an implant taken at different angles, for the purposes of determining the 3D seed distribution for intraoperative dose calculations\textsuperscript{156}. In that work, the cost of an assignment was related to the projective error of the match between two images given a third image. Reducing a task to a linear assignment problem is convenient because it can then be solved quickly and efficiently by linear programming techniques\textsuperscript{157}, or the Hungarian algorithm\textsuperscript{158}, the latter of which is used in this study.

The linear assignment is visualized in Figure 2.5 in terms of the analogous problem of computing a \textit{minimum weight bipartite matching} on the bipartite graph $G^b = (V^b, E^b)$. The vertices of this graph represent seeds from both the preplan and postplan, $v_i^a, v_i^b, v_j^b, v_j^b \in V^b$, with an edge $(v_i^a, v_j^b) \in E^b$ between every seed in the preplan and postplan. The graph $G^b$ is bipartite because every edge connects vertices in two distinct sets. A matching $E_{\text{match}} \subseteq E^b$ is any subset of edges which connect each preplan seed to a single postplan seed, and vice versa. A maximum matching is semantically equivalent to a correspondence, viz: $(v_i^a, v_j^b) \in E_{\text{match}} \iff \exists (a, i) (m_{ai} = 1)$. Thus, a maximum matching of a bipartite graph implies a correspondence between members of its disjoint sets. If each edge $(v_i^a, v_j^b)$ is assigned the weight $\Delta_{ai}^{\text{pos}}$, solving Eqn. (2.2) is equivalent to finding the matching with the minimum (summed) weight.

![Figure 2.5: Seed matching by linear assignment.](image)

(i) Two seeds from the three-strand example are shown.
(ii) The bipartite graph $\mathcal{G}$, with the preplan vertices on the left and the postplan vertices on the right. For clarity, only selected vertices are shown. Each edge in this graph is weighted by the respective positional correspondence error term.
(iii) The minimum weight maximum matching. Optimal correspondence matrix element $m_{ai}^{\text{opt}} \in \Delta^{\text{opt}}$ is one if $(a, i)$ is an edge in this matching.

Any assignment problem that can be expressed as a minimum weight bipartite matching problem is a linear assignment and vice versa. Although modifications to the relative weighting of the terms in Eqn. (2.2) will influence the resulting reconstruction, the problem remains linear as long as each edge weight depends only on those vertices the edge connects. In other words, an assignment problem is only a linear assignment
problem if the suitability of one assignment does not depend on the rest. This has two important consequences. First, optimizing the MD criterion, which has formed the basis of all plan reconstruction in studies hitherto, can be performed efficiently and optimally as a linear assignment. Second, a reconstruction metric in which the relationships between seeds, like spacing, are used to guide matching will not result in a linear assignment, because such comparisons are by definition between pairs of assignments.

Because MD reconstructions are relatively easy to compute, and can be designed to take into account axis-dependent uncertainty, it makes sense to take advantage of them to find the approximate correspondences necessary for the coarse registration in Step 1 rather than relying on the generic nearest-neighbor criterion of ICP. Also, since they are based on optimizing a similar model of correspondence likelihood to that of previous investigators, they will be used as a benchmark against which our method will be compared.

**Trajectory Angle Correspondence Error**

The second piece of information used to elicit correspondences in this study is the relative orientation of pairs of seeds. Simply put, a pair of seeds are more likely to be members of the same strand if they are connected by a line that is parallel to the $z$-axis, because that is the axis along which the template guides needles during implant. Recall that $\alpha_{ij}$ is the angle of divergence of vector $r_{ij}$ from this direction, and $l$ is a spacing index. The likelihood that a pair of seeds $i$ and $j$ are in the same strand is assumed to decrease as the angle it makes to its expected trajectory increases. This is quantified by the trajectory angle correspondence error $\Delta_{ijl}^{\text{traj}}$. Since all needles in the preplan have parallel trajectories, the trajectory angle correspondence error depends on the particular seeds $a$ and $b$ only inasmuch as $a$ and $b$ define the spacing.

$$\Delta_{ahbl}^{\text{traj}} = \Delta_{ijl}^{\text{traj}} = \frac{\alpha_{ij}}{sd_l^{\text{traj}}}$$  \hspace{1cm} (2.3)

The distribution of $\alpha_{ij}$ between connected seeds in the manual reconstruction depends on the spacing between them. Strands in the post-implant are often witnessed to have kinks, or exhibit greater deflections (splay) near the strand tip. The effects of this on $\alpha_{ij}$ tend to average out as the separation between seeds increases. This motivates normalizing the angle by $sd_l^{\text{traj}}$, the standard deviation of the spacing in the construction of the error metric. The standard deviation is estimated from the first 50 reconstructed cases (see Table 2.1).
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**Strand spacing correspondence error**

The last measure of the likelihood of seed correspondence is the strand spacing correspondence error \( \Delta_{\text{adj}} \). This quantity measures the extent to which the spacing between two seeds in the postplan vary from the spacing expected given the preplan seeds to which they correspond. The sample standard deviation of the postplan for the \( l^{th} \) spacing, \( sd_{l}^{\text{space}} \), was found from the first 50 test cases.

\[
\Delta_{\text{adj}} = \frac{\| r_{ab} \| - \| r_{ij} \|}{sd_{l}^{\text{space}}} = \frac{d_{ij} - \| r_{ij} \|}{sd_{l}^{\text{space}}}
\]  
(2.4)

The strand spacing correspondence error is the most specific of the error measures. Unlike the first two error terms, the variance in \( \Delta_{\text{adj}} \) for truly corresponding seeds pairs is largely independent of the effects of seed misplacement. The dominant source of strand spacing correspondence error for adjacent seeds in the same strand is segmentation precision, as inaccuracy in this regard (for example identifying the seed on the wrong slice) can introduce errors in measured seed separation that are a substantial fraction of the nominal spacing. At greater spacing, the effects of segmentation imprecision tend to average out. Instead, errors are principally attributable to the fact that strand curvature begins to undermine the straight-line model implicit in Eqn. 2.4. Nonetheless, the specificity of this measure to truly connected seeds is generally superior to the preceding error metrics.

**The Similarity function**

The main hypothesis of this study is that more accurate reconstructions are possible when inter-seed features which are quantified herein by the trajectory angle and spacing correspondence errors, are used to guide the reconstruction. All three error measures are combined in Eqn. (2.5) into the scalar *Similarity function*, which quantifies the likelihood of correspondence between seed pairs in the preplan and postplan as a value between zero and one. One indicates an ideal match.

The Similarity function is constructed as the product of monotonically decreasing functions of the error terms. The Similarity function is unitless, and it can be loosely interpreted as an unnormalized joint probability of the pair of correspondences \( a \leftrightarrow i \), and \( b \leftrightarrow j \). The form of the Similarity function was chosen to be a product of functions of the error so that large Similarity function values depend on feasibly small values for each of the error terms.

\[
s_{aibj} = \left( \frac{1}{1 + \left( \frac{\Delta_{\text{pos}}}{\beta_1} \right)^{\lambda_1}} \right) \left( \frac{1}{1 + \left( \frac{\Delta_{\text{adj}}}{\beta_2} \right)^{\lambda_2}} \right) \left( \frac{1}{1 + \left( \frac{\Delta_{\text{adj}}}{\beta_3} \right)^{\lambda_3}} \right) \left( \frac{1}{1 + \left( \frac{\Delta_{\text{adj}}}{\beta_4} \right)^{\lambda_4}} \right)
\]  
(2.5)
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The $\beta$ constants in Eqn. (2.5) are model parameters which control the rate of roll-off in the factors, weighing the relative importance of each type of error in deciding the likelihood of correspondence. Throughout this paper we have adopted the convention of explicitly denoting parameters which were found by trial-and-error with $\beta$ labels. In Eqn. (2.5) these parameters are used to improve the sensitivity and specificity of the Similarity function to correct reconstructions, and other investigators may benefit from tuning these values to their data. With that said, please note that the results of all 70 reconstructed cases in this study reflect a single setting of all $\beta$ parameters, which are compiled in Table 2.2.

Potential connections between seeds $i$ and $j$ in the postplan are screened by a maximum threshold on the trajectory angle $\alpha_{\text{max}}^\text{post}$, and a maximum threshold $d_{\text{max}}^\text{post}$ on the discrepancy between the seed spacing $r_{ij}$ and the set of possible planned seed spacings. These are the 99th percentile values computed from the first 50 test cases, and are in Table 2.1.

$$e_{ij}^\text{post} \geq 1 : \alpha_{ij} < \alpha_{\text{max}}^\text{post} , \exists l : |d_l - |r_{ij}| < d_{\text{max}}^\text{post}$$

(2.6)

These minimum requirements help trim clearly incorrect seed connections from consideration. The minimum ‘confidence’ (the $e$ value) in any connection that meets these criteria is one. Confidence values greater than one are reserved for the connections identified during the strand segmentation in the next section.

Formally, an $S$-reconstruction of a plan, denoted $M^S$, is defined to be the correspondence that maximizes the aggregate Similarity for all possible pairs of seeds:

$$M^S = \arg \max \left\{ \sum_{a}^{N} \sum_{i}^{N} \sum_{b}^{N} \sum_{j}^{N} m_{ai}m_{bj}e_{ab}^\text{pre}e_{ij}^\text{post}s_{abij} \right\}$$

(2.7)

The strand connectivity and connectivity confidence elements $e_{ab}^\text{pre}$ and $e_{ij}^\text{post}$ ensure that only the similarity between seeds pairs within strands (or potential strands) contribute to the sum.

Eqn. (2.7) is perhaps more intuitively understood in terms of a weighted subgraph matching problem. Subgraph matching involves finding the best representation of one graph inside another, for example as illustrated in Figure 2.6. In weighted subgraph matching, the quality of the match is quantified by the sum of the weight of the subgraph edges, each of which reflects how similar the edge is to the model edge it represents.
Graph and subgraph matching techniques are widely used in the fields of computer vision and pattern recognition to simplify the comparison of objects. The basic idea is to use a graph to distill the objects into a set of characteristic relationships between salient features, and reduce the comparison of the objects into a comparison of their graphs. The choice of features to abstract is critical, and is usually informed by specific expectations of how noise in the application corrupts the data acquisition or comparison process. For example, in one biometric fingerprint analysis method, graph vertices are used to encode the positions of fingerprint ridges, and edges describe whether the ridges are adjacent, or in intersection. This topological representation is robust to the continuous deformation, displacement, or rotations that would be expected during the collection of fingerprints from substrates gripped or otherwise contacted in an arbitrary orientation, and with different amounts of force.

The formalism of graph matching can be applied quite easily to describe plan reconstruction by defining a pair of graphs representing the preplan and postplan, \( G^{\text{pre}} = (V^{\text{pre}}, E^{\text{pre}}) \) and \( G^{\text{post}} = (V^{\text{post}}, E^{\text{post}}) \), which we are trying to match. The preplan graph vertices represent seeds from the preplan, \( v_a, v_b \in V^{\text{pre}} \), and the postplan graph vertices represent seeds from the postplan, \( v_i, v_j \in V^{\text{post}} \). The edges between the vertices represent strand structure and thus \( e^{\text{pre}}_{ab} \) and \( e^{\text{post}}_{ij} \) can be understood to indicate edges in the pre- and postplan graphs: \( (v_a, v_b) \in E^{\text{pre}} \) iff \( (e^{\text{pre}}_{ab} = 1) \) and \( (v_i, v_j) \in E^{\text{post}} \) iff \( (e^{\text{post}}_{ij} \geq 1) \).

In this paradigm, a given correspondence matrix \( M \) defines a subgraph match of the preplan graph in the postplan graph. The edges in this subgraph are weighted by the Similarity function term associated with the seeds that it connects. That is, if the correspondence implies that preplan graph edge \( (v_a, v_b) \) is the subgraph edge \( (v_i, v_j) \), that edge has weight \( s_{\text{subj}} \). Thus, the Similarity function can be interpreted as describing the similarity between edges in the graphs, and Eqn. (2.7) as describing the fitness of a particular subgraph match in terms of the summed weight of its edges. This can be made explicit by performing the summation over the graph edges as in Eqn. (2.8).

\[
M \rightarrow \text{subgraph of weight} = \sum_{(v_a, v_b) \in E^{\text{pre}}} \sum_{(v_i, v_j) \in E^{\text{post}}} m_{ab} m_{ij} s_{\text{subj}} \tag{2.8}
\]
Figure 2.7 illustrates the weighted subgraphs of the two reconstructions of the three-strand example introduced in Figure 2.2. The thicknesses of the lines representing the edges in the subgraph match are used to denote their weight. Note that for the poorer reconstruction, some of the connections implied by the reconstruction do not have edges in the postplan graph, because it is assumed that these edges do not satisfy Eqn. (2.6). The weight of these in the subgraph is therefore zero.

Unfortunately, Eqn. (2.7) and its associated weighted subgraph matching problem are NP-hard quadratic assignment problems\(^{161,162}\). In contrast to plan reconstruction by Eqn. (2.2), no efficient algorithms for finding or verifying the optimal solution for such problems have yet been discovered\(^{163}\). Global optimization techniques for quadratic assignment problems of \(N \approx 100\) assignments are prohibitively slow\(^{162}\) and unsuited to a clinical implementation of plan reconstruction where the reconstructions need to be performed routinely. Consequently, an approximation method is used to find solutions in a reasonable amount of time. However, before undertaking to solve the weighted subgraph matching problem given by Eqn. (2.7), the \(S\)-reconstruction algorithm takes a detour in which it first attempts to discover probable strand structures in the postplan.

![Subgraph Matches](image)

Figure 2.7: Weighted subgraph matches of the two reconstructions of the three-strand example implant (see Figure 2.2 for the seed distributions). Weighting is given by the Similarity function. Only the edges between adjacent seeds are shown for clarity. In the poor match, the edges implied by the preplan connections \(5 \rightarrow 6\) and \(6 \rightarrow 7\) do not have corresponding edges in the postplan graph and thus do not contribute to the total subgraph weight.

### 2.2.6 Step 2: Strand Segmentation by Minimum Cost Flow

A minimum cost flow\(^{152,164,164}\) (MCF) technique is used to approximately classify seeds of the postplan into strands. The concept of flow through a directed graph or network has its roots in transport problems, in which the goal might be to determine how to transport goods from factories to outlets such that the total cost of transportation in minimized. Typically, the problem is constrained by the supply and demand of goods at each facility, and the capacity of the transit routes between them. The aim of this section is to cast strand segmentation as an MCF problem.
Consider again the graph representation of the three strand example. Note that the edges between adjacent seeds in strands comprise $K$ disjoint paths through the graph which traverse each vertex exactly once. The main intuition is that with the right cost definition, these paths can be construed as the $K$ ‘routes’ of lowest cost that collectively pass through all seeds from the apex to the base, and recovered by solving a minimum cost flow problem.

To do this, a postplan flow graph $G^{\text{flow}} = (V^{\text{flow}}, E^{\text{flow}})$ is created on which the costs of flow will be defined. This graph is similar to the postplan graph $G^{\text{post}}$, and is comprised of vertices $v^{\text{flow}} \in V^{\text{flow}}$ representing postplan seeds. However, edges in the flow graph are only defined between seeds which are potentially neighbors in a strand, directed superiorly with respect to the seeds’ $z$ coordinates. The postplan flow graph also includes two special vertices which are called the source and the sink, where flow will enter and exit the graph. A set of directed edges connects the source to each seed, and each seed to the sink: $(v^{\text{source}}, v_i), (v_i, v^{\text{sink}}) \in E^{\text{flow}} : \forall i = 1...N$. The flow is represented by an integer function of each vertex, and can be positive (the vertex supplies flow), negative (the vertex demands flow), or zero (flow is conserved). Flow is only permitted to travel in the same direction as the edge it is passing through. Each edge has a specified capacity, the maximum quantity of flow permitted through the edge.

To compute the strand segmentation, a linear program is set up with the sink demanding $K$ units of flow from the source, which is constrained to be delivered along the edges between seeds. Each edge has unit capacity, and one unit of flow must cross all seed vertices. For every unit of flow transported along an inter-seed edge, there is an associated cost.

Ideally, the MCF cost function would be designed so that the cost of flow along each inter-seed edge depends on which seed connection the edge represents. Of course, this begs the question; computing the correspondence is the problem! Thus, while the set of possible spacings between adjacent seeds can be enumerated from the preplan, and any variation in trajectory angle can be treated equally without reference to a particular correspondence, the spacing between any two particular seeds in the postplan cannot. To address this, the cost of flow along each edge must be robust to the possibility that it could correspond to many possible spacings.

To define the cost, let $\Lambda \subset 1...L$ be the subset of the spacing indices corresponding to the possible adjacent spacings for the plan, which is known. In BCCA plans, in which most strands are uniformly loaded, with perhaps one or two ‘special loads’ (See Section 1.2.4), $|\Lambda|$ is typically between one and three (in the three strand example, $|\Lambda| = 2$, the two-seed strand has a longer spacing). Let $\lambda \in \Lambda$ be a possible adjacent spacing index for the plan. Using these definitions, the cost is:
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\[ c_{ij} = (1 + \beta_7 \lambda) \cdot \min \left\{ \left( 1 + \frac{\Delta_{ij}^{\text{traj}}}{\beta_3} \right)^{\gamma_i}, \left( 1 + \frac{\Delta_{ij}^{\text{space}}}{\beta_5} \right)^{\gamma_i} \right\} : \forall (\lambda \in \Lambda) \quad \forall (v_i^{\text{flow}}, v_j^{\text{flow}}) \in E^{\text{flow}} \]  

(2.9a)\[
c_{i,\text{source}} = c_{\text{sink},j} = 1 \quad \forall (v_{\text{source}}, v_i), (v_i, v_{\text{sink}}) \in E^{\text{flow}}
\]  

(2.9b)

The cost function penalizes flow between seeds with large trajectory and spacing correspondence errors. The flow cost between any two seeds \(i\) and \(j\) is the minimum of the costs evaluated at each spacing \(\lambda\). In other words, it is assumed that an edge represents a connection at whichever spacing results in the smallest error terms. The purpose of factor \((1 + \beta_7 \lambda)\) is to bias flow away from edges representing higher spacings if there is an alternate edge of similar quality at a shorter spacing. This is because shorter spacings are generally more prevalent, especially in implants done at the BCCA. By way of example, suppose there are two possible edges for flow to exit a particular seed, each representing a connection at a different spacing. If both of these edges represent a connection with the same error values, the connection at the more prevalent spacing is probably the one which is correct, and so it is given a lower cost. This particular factor is specific to the BCCA loading style, but the construction of a function to serve a similar purpose for a different spacing prevalence distribution would be straightforward.

The solution to the MCF problem is the set \(E^{*\text{flow}}\), the edges used by the minimum cost flow. The asterisk is used to denote that it is the optimal set of edges. The optimization is performed using a flow specific linear program solver in the MATLOG toolbox (http://www.isc.ncsu.edu/kay/matlog) for MATLAB (The Mathworks, Natick, MA). The seeds corresponding to strands are implied by the \(\kappa = 1...K\) subsets of edges in \(E^{*\text{flow}}\) that form a path from source to sink. A graph schematic of this process is shown in Figure 2.8.

Once likely strands have been extracted from the postplan, a correspondence is computed by modifying Eqn. (2.2) to perform an assignment of \(K\) strands rather than \(N\) seeds. To do this, an analogue of the positional correspondence error is defined for strands to match them based on their expected positions. The position of a strand is taken to be the mean position of the seeds that comprise the strand. Let \(\mathbf{r}^{\text{strand}}_k = (x^{\text{strand}}_k, y^{\text{strand}}_k, z^{\text{strand}}_k)\) and \(\mathbf{r}^{\text{strand}}_\kappa = (x^{\text{strand}}_\kappa, y^{\text{strand}}_\kappa, z^{\text{strand}}_\kappa)\) be the positions of the \(k^{\text{th}}\) and \(\kappa^{\text{th}}\) strands. The positional (strand) correspondence error of the strand assignment \(k \leftrightarrow \kappa\) is defined analogously to Eqn. (2.1) using the same axis weights.

\[ \Delta_{k\kappa}^{\text{pos,strand}} = \sqrt{\left( \frac{x^{\text{strand}}_k - x^{\text{strand}}_\kappa}{sd^x} \right)^2 + \left( \frac{y^{\text{strand}}_k - y^{\text{strand}}_\kappa}{sd^y} \right)^2 + \left( \frac{z^{\text{strand}}_k - z^{\text{strand}}_\kappa}{sd^z} \right)^2} \]  

(2.10)
The strands can then be matched by substituting Eqn. (2.10) for the positional (seed) correspondence error in Eqn. (2.2) and solving the linear assignment.

After the strands are matched, the identity of each seed can be deduced providing the correct number of seeds is found in the strand. If this is the case for all strands, the plan reconstruction process is terminated as the reconstruction derived from this correspondence is unlikely to be improved by recourse to graph matching. However, because strand segmentation by MCF does not involve any ascription of identity to the vertices, it is quite common after matching the strands by position to find that they have the incorrect number of seeds. An example of how this might occur is illustrated in Figure 2.9. This was found to be a common pitfall of other line fitting techniques that were explored as alternatives to the MCF technique.
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Even if strand matching does not result in a correct correspondence, computing $E^{flow}$ offers valuable insight into the structure of the postplan which facilitates the subgraph matching process. The paths of minimum cost flow always imply the correct number of strands and connect all seeds, even if this means that flow must be sent along a high-cost edge. This often indicates that such connections are correct, although they tend to be missed if subgraph matching is performed directly because they do not substantially influence the subgraph weight. This can result in the subgraph matching algorithm discussed in the next step to become trapped in local minima. Performing strand segmentation first helps to mitigate this by emphasizing the postplan edges associated with likely strand connections.

Our increased confidence in the edges of $E^{flow}$ is asserted through the values of the postplan strand connectivity confidence terms $e_{ij}^{post}$, which are coefficients of the Similarity associated with those edges in Eqn. (2.7). The effect is to increase the weight of any subgraph composed of these edges, irrespective of the seed correspondence the graph may imply. This agnosticism towards seed correspondence is consistent with the limitations inherent in the MCF method.

\[
e_{ij}^{post} = \begin{cases} 
\beta_k & \exists (i, j) : (v_i^{post}, v_j^{post}) \in E^{flow} \\
1 & \exists (i, j) : (v_i^{post}, v_j^{post}) \in \{E^{post} \setminus E^{flow}\} \\
0 & \text{otherwise}
\end{cases}
\]  

(2.11)

The confidence factor $\beta_k > 1$ was, like all beta values in this study, set by trial and error to maximize algorithm accuracy during testing.

2.2.7 Step 3: Subgraph Matching by Graduated Assignment

In this step, we return to the difficult issue of solving the quadratic assignment (Eqn. (2.7)), with the confidence weighted connectivity terms derived from the strand segmentation in hand. To do this, a nonlinear optimization algorithm called Graduated Assignment\[165\] is used. It is one of many approximation-generating combinatorial optimization techniques which could have been applied, such as simulated
annealing\(^{166,167,168}\) or genetic algorithms\(^{169}\), and as such there is no guarantee that an optimal solution will be found. Graduated Assignment was selected because it is fast, flexible, and reasonably easy to implement. The algorithm is treated in some depth here because it is the only component of \(S\)-reconstruction for which the quality of the result is sensitive to the parameterization of the optimization routine itself. However, this discussion is not intended to be comprehensive, so please see the reference for greater detail.

Graduated assignment is an iterative process in which an estimated correspondence/assignment is used to form a linear approximation to the quadratic problem. In each iteration, this is solved to yield a better solution, which informs the linearization of the next iteration. These steps occur in tandem with a system of graduated non-convexity in which an annealing parameter is used to smooth differences in the weights of the edges of the bipartite graph associated with the linear assignment problem that arises from the linear approximation. The algorithm also relaxes the binary constraints on the correspondence matrix to allow fractional correspondences, permitting smoother transitions between assignments.

Let the relaxed correspondences between seeds be represented by the doubly stochastic matrix \(\tilde{M}\) whose estimate at iteration \(n\) is \(M^{n-1}\). All elements of a doubly stochastic matrix are between zero and one, and its rows and columns all sum to one. This implies that assignment is ‘conserved’; the sum of the fractional assignments of any particular seed to the others is always one. In this study the algorithm is initialized with the MD reconstruction correspondence \(M^{MD}\) found by Eqn. (2.2). The linear approximation using the estimated correspondence is performed as follows, where \(\tilde{m}_{ai}^{n-1} \in \tilde{M}^{n-1}\):

\[
s_{bij}^n = \sum_a \sum_i \tilde{m}_{ai}^{n-1} e_{ab}^{pre} e_{ij}^{post} s_{abj}
\]

(2.12)

This is a first order Taylor series expansion of the quadratic objective around \(\tilde{M}^{n-1}\). Intuitively, the value \(s_{bij}^n\) describes the ‘utility’ of the assignment \(b \leftrightarrow j\) given the current state, and it may be helpful to visualize Eqn. (2.12) as a voting process, where each seed \(a\) that is stranded to \(b\) is entitled to ‘vote’ for the assignment \(b \leftrightarrow j\). Each vote has value \(s_{abj}\) which is weighed by the confidence that the postplan seeds are connected (\(e_{bij}^{post}\)) and the current state-of-belief that \(a \leftrightarrow i\) (\(\tilde{m}_{ai}^{n-1}\)). The sum \(s_{bij}^n\) is thus the sum of votes, which may be fractional, for seed \(b\) to be assigned to \(j\).

To smooth differences in assignment utility during early iterations, the assignment utilities are exponentiated using an iteration dependent annealing parameter \(\tau(n) > 0\), and parameter \(\beta_0\).

\[
q_{bij}^n = \exp \left( \tau(n)\beta_0 s_{bij}^n \right)
\]

(2.13)
Elements $q^n_{bj}$ are the smoothed assignment utilities. It can easily be shown that Eqn. (2.13) approaches one for any value of $s^n_{bj}$ as $\tau$ approaches zero, and a given difference in utility between different assignments is a monotonically increasing function of $\tau$. Thus for small values of $\tau$, all assignments appear equally attractive, and for large values the algorithm becomes increasingly discerning of small differences in utility. In this study, the following annealing schedule was used.

$$\frac{\tau(n+1)}{\tau(n)} = \beta_1, \quad \beta_{11} < \tau(n) < \beta_{12}$$

(2.14)

The parameters were selected by trial-and-error to maximize reconstruction accuracy on a set of test cases, which is described in the next section. The computational efficiency of Graduated Assignment is due to the fact that finding an optimal correspondence which maximizes these annealed values is an efficient linear assignment problem (‘argmax’ is short for ‘the argument that maximizes’).

$$\tilde{M}^n = \arg \max \left\{ \sum_{b} \sum_{j} \tilde{m}_{bj} q^n_{bj} \right\}$$

(2.15)

Note that this differs slightly from Eqn. (2.2) in that it is a maximization, and that the domain is a relaxed correspondence which permits fractional assignments. Nonetheless, Eqn. (2.15) is linear, and is straightforward to solve using the softassign algorithm, thus yielding the updated estimate of the correspondence. As the algorithm proceeds and the annealing parameter grows, the relative differences in the utility of different assignments are more strongly emphasized, which tends to drive the solution of Eqn. (2.15) towards a binary correspondence matrix as desired. This process is called ‘deterministic annealing’ and is thought to convexify the objective space and allow the algorithm to escape local minima. A schematic illustrating how Graduated Assignment is composed of a loop of linear assignments is provided in Figure 2.10.

Graduated Assignment terminates when the annealing parameter reaches its upper bound. Typically, the optimized correspondence matrix is approximately binary. However, this is not guaranteed, and in this study any postplan seed assigned at a fraction of <50% is left unassigned and passed to the user to manually correct using the graphical interface. A flowchart summarizing the complete $S$-reconstruction algorithm is shown in Figure 2.11.
2.2.8 Evaluation of the S-reconstruction Algorithm

Reconstruction accuracy

To compare the relative effectiveness of automatic plan reconstruction using the proposed method, S-reconstructions are compared to MD reconstruction using three measures. The first is the assignment accuracy, the percentage of correctly corresponding seeds:

\[
\text{Assignment Accuracy} \% = \left( \frac{\text{number of correctly corresponding seeds}}{N} \right) \times 100
\]

Second, the needle assignment accuracy is the percentage of seeds correctly assigned to their needle or strand:

\[
\text{Needle Assignment Accuracy} \% = \left( \frac{\text{number of seeds correctly assigned to needle}}{N} \right) \times 100
\]

Needle assignment accuracy is useful to gauge the extent to which seeds are mistaken for their strand neighbors, as when this occurs it impacts assignment accuracy, but not needle assignment accuracy.

Lastly, the percentage of seeds correctly connected to their intra-strand neighbors is computed. Given the correct postplan subgraph edge set \( E \) from manual reconstruction, if \( E' \) are the edges corresponding to the subgraph implied by the reconstruction, the connectivity accuracy is:

\[
\text{Connectivity Accuracy} \% = \left( \frac{|E' \cap E|}{|E|} \right) \times 100
\]
Connectivity accuracy helps to distinguish when strands are wrongly identified, but correctly connected, as when one strand is mistaken for another. Manual correction is easier and less time consuming to perform when needle assignment and connectivity accuracies are higher.

Of the 70 test cases in this study, the manual reconstructions of 50 were used during the development of the algorithm in order to find effective settings for the $\beta$ parameters, and to compute standard deviations to weigh the error metrics. To demonstrate the extent to which bootstrapping parameters from the test dataset biased the performance of the algorithm, the remaining twenty cases were appended to the dataset after the algorithm parameters were fixed. The mean assignment, needle assignment and connectivity accuracy metrics of these cases are reported independently. All reconstruction accuracies are given plus/minus one standard deviation, and the significance level is 0.05 for statistical tests.

Factors affecting performance

Previous investigators found that the principal factor affecting reconstruction accuracy was seed density, arguing that as the mean distance between seeds approaches the mean positional error, seeds are more likely to be mistaken for their neighbors. Assignment accuracy, in other words, was found to be inversely proportional to seed density. To assess this effect, the seed density, defined as the total number of seeds divided by the PTV volume, was computed for all plans in this study. Robust linear fits were performed to search for a density effect, defined as a significant difference of the trendline from a slope of zero.

It may be argued that the average density is too crude, and that it is the effects of local seed clusters that impact accuracy. To measure the effect of clustering on assignment error, the mean number of seeds within spheres of radius 5 and 10 mm centered on each seed was computed and compared between correctly and incorrectly assigned seeds. The influence of the number of seeds with a lower positional correspondence error than the truly corresponding seed on reconstruction accuracy was also examined.
### Table 2.1: Implant measurements from the first 50 test cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( sd^x )</td>
<td>2.7 mm</td>
</tr>
<tr>
<td>( sd^y )</td>
<td>2.9 mm</td>
</tr>
<tr>
<td>( sd^z )</td>
<td>4.2 mm</td>
</tr>
<tr>
<td>( sd_{maj} )</td>
<td></td>
</tr>
<tr>
<td>( l = 1 )</td>
<td>6.4°</td>
</tr>
<tr>
<td>( l = 2 )</td>
<td>5.1°</td>
</tr>
<tr>
<td>( l = 3 )</td>
<td>4.3°</td>
</tr>
<tr>
<td>( l = 4 )</td>
<td>3.7°</td>
</tr>
<tr>
<td>( l = 5 )</td>
<td>3.3°</td>
</tr>
<tr>
<td>( l = 6 )</td>
<td>3.2°</td>
</tr>
<tr>
<td>( sd_{safe} )</td>
<td></td>
</tr>
<tr>
<td>( l = 1 )</td>
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</tr>
<tr>
<td>( l = 2 )</td>
<td>3.8 mm</td>
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<tr>
<td>( l = 6 )</td>
<td>2.0 mm</td>
</tr>
<tr>
<td>( \alpha_{max} )</td>
<td>54°</td>
</tr>
<tr>
<td>( d_{max} )</td>
<td>4.6 mm</td>
</tr>
</tbody>
</table>

Table 2.2: Algorithm parameters, determined by trial-and-error to maximize reconstruction accuracy in the first 50 test cases

<table>
<thead>
<tr>
<th>( \beta )</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>3</td>
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<td>0.1</td>
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<td>1.5</td>
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<td>10</td>
</tr>
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<td>10</td>
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</tr>
<tr>
<td>11</td>
<td>0.05</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 2.1: Implant measurements from the first 50 test cases
Chapter 2 – Plan Reconstruction

2.3 Results and Discussion

2.3.1 Comparison of Accuracy

Significant gains in accuracy were hypothesized to be achievable by introducing strand specific features into plan reconstruction. The methodology presented describes the steps necessary to obtain robust results across a test set of 50 cases. To justify the additional computational resources required to assess correspondences on the basis of inter-seed features, \( S \)-reconstructions were compared on a case by case basis with reconstructions derived directly from Eqn. (2.2), which are referred to as MD reconstructions since they essentially minimize the summed distance between corresponding seeds. Although the metric being optimized is similar to that of Archambault et al., the Hungarian algorithm was used instead of simulated annealing, and the datasets and implant techniques are different. Therefore, while the results of this study are suggestive of the limitations of only using a minimum distance criterion, it cannot be discounted that their implementation on our dataset might produce better results.

The proposed method resulted in an improvement in mean assignment accuracy from 85.2±0.2% for MD reconstructions to 97.7±0.4%. Fifty-two of the 70 \( S \)-reconstructed cases were completely error free, compared to 19 of the MD reconstructions. The mean assignment accuracy of the \( S \) (vs. MD) reconstructions for the subset of cases that had at least one error was 91.1±0.4% (71±17%), with a minimum assignment accuracy of 74.0% (32.0%). In these cases, the mean needle accuracy was 96.7±0.3% (85±8%), with mean connectivity accuracy of 97.0±0.2% (78±11%). The histograms in Fig.

![Diagram](attachment:image.png)
2.12 show the improvement in assignment, needle assignment, and connectivity accuracy of S-reconstruction over MD reconstructions for all 70 cases. For assignment accuracies ranging from 85-95%, seeds in S-reconstructions are always more accurately connected, a trend which it is not unreasonable to believe will extrapolate to more difficult cases that may be encountered clinically. 

For the subset of twenty cases which did not influence the $\beta$ parameters of the reconstruction algorithm, the mean assignment accuracy (vs. remaining 50) was 97.6±0.7% (97.8±0.4%), the mean needle assignment accuracy was 98.9±0.3% (99.1±0.2%), and the mean connectivity accuracy was 99.1±0.2% (99.3±0.1%). This suggests that the algorithm does not suffer from being over-fit to the training dataset, at least for implants performed at this center.

A common mode of error when needle assignment accuracy was high was for terminal seeds at the opposite ends of two strands to be swapped, with a mis-assignment of seeds along each strand with their neighbors. Where connectivity accuracy was high, but needle assignment accuracy low, the tendency was for whole strands to be misidentified for each other. This is observed to occur between strands in the postplan that are proximate, have similar seed counts, and for which it appears after registration that each was implanted at the planned depth of the other. These two types of errors account for virtually all mistakes in S-reconstructions. In contrast, the errors in MD reconstructions are typically not strand-preserving. These distinctions are important from a practical perspective. For a given rate of error, a high degree of connectivity accuracy paints a more coherent picture of how the prostate deformed during the needle insertions, which makes interpreting and correcting the reconstruction far easier.

2.3.2 Factors Relating to Reconstruction Accuracy

No significant correlation between the mean number of seeds (p=0.75), nor the mean number of needles (p=0.61) on assignment accuracy was found. For both S and MD reconstructed cases, average seed density also had no effect on assignment accuracy with linear fit slopes not significantly different from zero (p=0.55 and 0.67 respectively). In the cluster analysis, using a radius equal to the mean difference from expected position of 5 mm, no effect was found. Increasing the radius to 10 mm resulted in the detection of a small but significant effect for the MD method, with the mean number of seeds in the subvolume being 4.1 for correctly identified seeds, versus 5.4 for those incorrectly identified (p<0.01). No effect was found for S-reconstructions at either radius. Linear regression on seed and needle counts were similarly non-explanatory.
A consequence of the assumption that smaller positional correspondence errors imply a greater likelihood of correspondence is that seeds which deviate substantially from their planned positions are less likely to be accurately assigned. However on logistic regression, a correlated value, the number of interposing seeds between a correct seed and its planned position, in a Euclidean sense, is an even better predictor. A mean of 5.7 interposing seeds was found for incorrectly identified seeds, compared to a mean of 0.6 for those correctly identified. The binomial probability of a successful seed assignment in S reconstruction falls from 96% (CI_{95%}=95-96%) when there are three interposing seeds to 44% (CI_{95%}=35-53%) when there are ten. In comparison, the accuracy of MD reconstruction, which is expected to be highly sensitive to this, fell to 43% (CI_{95%}=37-49%) for only three interposing seeds. In the BCCA dataset, the overall mean number of interposing seeds is 0.7, and 95% of seeds have three or fewer. Note that the number of interposing seeds is primarily a function of misplacement, edema, and migration. This suggests that seed density only becomes an effect when it sufficiently exacerbates the number of interposing seeds given the existing degree of placement uncertainty.

Fig. 2.12: A comparison of S-reconstruction vs. MD reconstruction accuracy. Histograms of assignment accuracy (top left), needle assignment accuracy (top), and connectivity accuracy (left) are contrasted for the 70 test cases. The cases are sorted from left to right in descending order of assignment accuracy.
2.3.3 S-reconstruction of Other Implant Styles

The multi-step algorithm that has been proposed herein was developed specifically to address the
reconstruction of stranded implants, in which inter-seed spacing, and possibly strand trajectory are better
conserved with respect to the preplan. In stranded implants, seeds within a train are misplaced and migrate
as a group; if there is an error in the placement of one seed, there is a systematic error in the placement of
them all. Thus, the motivation for this work was to shift the focus from a reconstruction metric based on
the expected position of a postplan seed to one based on inter-seed constraints. However, the resulting
mathematical formalism of graph matching can be generalized to any implant, and there is no reason in
principle that a stranded implant with predominantly non-uniformly spaced seeds, or even a loose seed
implant could not be reconstructed by the graph matching techniques that have been described.

The planning style at the BCCA results in a majority of strands which are composed of uniformly spaced
seeds. However, it does not necessarily follow that these are simpler to reconstruct than plans with
predominantly non-uniform loads. Roughly speaking, the latter will have a more distinct preplan graph
‘signature’, for which there will be fewer high weight subgraph permutations in the postplan graph. This is
because the specificity of the strand spacing correspondence error term of the Similarity function to
mismatches between neighbors is poor when the spacing is uniform (Figure 2.13 (i,ii)). This problem is
compounded when there is an apparent translation between corresponding pre- and postplan strands,
because the periodicity of a uniformly loaded strand means that seeds will simultaneously appear as good
potential matches for their neighbors (Figure 2.13 (iii)). Such translations in non-uniformly loaded strands
will typically produce a much smaller group of spurious alignments.

![Figure 2.13](image)

Figure 2.13: Seeds in a uniformly loaded strand are more easily mismatched with their
neighbors. In this example, the strand spacing correspondence error in the uniformly spaced
strand in (i) is poorly specific to the correct matching. In contrast, that error is small for only
two possible matches in the non-uniformly loaded strand in (ii). In (iii), two possible relative
translations of a uniformly loaded strand result in highly weighted incorrect matches for three
of the four seeds.

As mentioned earlier, the cost function in the computation of minimum cost flow would have to be
modified to reflect differences in the prevalence of spacing for different implant styles. In general, it is
reasonable to expect that MCF methodology would be slightly less effective with a greater variety of
possible adjacent spacings, because this implies a larger array of low cost edges leaving each seed vertex,
and more low-cost feasible flows. When this is the case, it is possible that there is poorer coincidence between the minimum cost flow and the correct strand structure. Whether or not greater uncertainty in the strand connections going into the graph matching step would offset the expected improvement in the specificity of the Similarity function will have to be established by future analysis.

S-reconstruction may even be viable for loose seed implants. Although there is no physical constraint between them, loose seeds still have a planned spacing which the oncologist is presumably trying to maintain while depositing the seeds. Any success in exploiting this structure depends on the extent to which spacing can be maintained during delivery, which is precisely the question that the availability of plan reconstruction algorithms may help to answer in the future. Widely performed comparisons between the dosimetry of loose and stranded seed implants\textsuperscript{85,103,104,170,171} indirectly suggest that the integrity of planned inter-seed spacing in a loose seed postplan is comparable to that of a stranded seed implant in as much as it is sufficient to meet coverage goals. Of course, the link between high quality dosimetry and accurate seed placement is clouded by the robustness of varying planning styles, the effect of edema, and contour variability, all of which influence dosimetric quality. Yet, there are few direct comparisons between the accuracy of loose and stranded seed placement from which to base speculation. In one small study, investigators found similar values in the average radial deviations from the planned positions of loose and stranded seeds which were implanted on opposite sides of the gland in each of a series of 8 patients\textsuperscript{150}.

On the balance, current evidence does not seem to contradict the position that loose seed implants retain at least some of their planned structure, and it is possible that graph matching methodology can be adapted to exploit this. This is not a claim that S-reconstruction, using the parameters reported herein, will achieve the same levels of performance on loose seed implants that have been demonstrated on the BCCA dataset. However, a modified graph matching approach may improve on existing alternatives.

### 2.3.4 Computational Performance

The plan reconstruction algorithm and interface are prototyped in MATLAB. The non-optimized code takes approximately 5-10 seconds on an average desktop computer, most of which is due to the annealing phase of Graduated Assignment. Although MD reconstruction via the Hungarian algorithm is essentially instantaneous, the time necessary to manually correct mistakes is far longer than this difference in computation time. The issue of scaling to large number of seeds has not been addressed, which may be perceived as a shortcoming of this fundamentally combinatorial technique. However, the future of PIPB is probably not in implants with sufficient seeds for this to become a practical concern. Indeed, most recent evidence indicates a trend in interest towards implants with fewer, higher activity seeds\textsuperscript{172,173}. 

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2.4 Conclusions

In this chapter, a technique for stranded plan reconstruction is demonstrated which takes advantage of the delivery characteristic in which there is the smallest uncertainty, the inter-seed spacing along strands. By casting plan reconstruction as a graph matching problem between the planned and delivered seed distributions, and applying a combination of optimization techniques, improvements in the accuracy of plan reconstruction for stranded implants can be achieved. An important specific contribution of this work is the recognition that solving the difficult quadratic assignment problem which underlies the graph matching process using a fast approximation algorithm often yields excellent results if the problem is first informed by the results of a low-complexity strand segmentation task. In all cases analyzed, the proposed method was found to produce more accurate reconstructions than when only a summed distance error metric was minimized. When the algorithm fails, it fails gracefully, providing partial reconstructions in which the vast majority of seeds are correctly connected. A user interface has been created with which physicists can manually verify and correct errors in reconstruction in a clinical setting.

Many new areas of research which might otherwise be onerous are realistic given the availability of easy, on-demand plan reconstruction. The method described in this paper is currently being used to assess the extent of strand migration due to edema, the efficacy of using additional discretionary seeds intraoperatively, and the feasibility of post-implant analysis of mixed-activity implants. This technology has been introduced into the clinic for the purpose of verifying seed segmentation, as the existence of a feasible reconstruction is strong evidence for the validity of that segmentation. Visualizations of reconstructed plans such as Figure 2.1 give oncologists the opportunity to examine post-implant strand trajectories, and appreciate the consequences of needle deflection and prostate deformation in a way that is not possible from the seed cloud alone. Automatic plan reconstruction has the potential to facilitate many important improvements in PIPB.
Chapter 3 - Determining the Orientation of Implanted Seeds

3 Determining the Orientation of Implanted Seeds

3.1 Introduction

The physical structure of brachytherapy seeds induces fluence anisotropy. This is taken into account in the American Association of Physicists in Medicine (AAPM) TG-43 formalism\textsuperscript{81} for the calculation of dose from brachytherapy sources, which provides sets of factors for different seed models. The TG-43 dose calculation is subdivided into 1D and 2D formalisms, where the former averages the effects of anisotropy and non-point activity distributions over all possible orientations of the implanted seed, to arrive at an expression for dose rate which depends only on distance. For prostate implants, use of the 1D formalism is common practice, since determining seed orientations directly from CT images is problematic. However, the recent AAPM TG-137 report\textsuperscript{88} recommends the use of the 2D dose calculation formalism, citing improved accuracy at the distances relevant in prostate implants. The treatment planning software used for PIPB at our institution (VariSeed 8.02, Varian, Palo Alto, CA) supports the 2D formalism, but the software assumes that all seeds are aligned with the CT axis.

The implicit assumption in applying the 1D formalism is that the probability distribution describing the orientation of each implanted seed is uniform; in other words, all orientations are equally likely. However, there is evidence that even loose seeds tend to be oriented in the approximate direction of the inserted needle\textsuperscript{174}. At the BCCA, stranded seeds are used which restrict the pose of implanted seeds. Seeds remain well aligned with the needle tracks when such stranded materials are used, since seeds are not free to rotate after the needle is removed. Thus, the 1D formalism will be an even poorer approximation of a stranded seed dose distribution than of a loose seed one.

The aim of this study was to develop a method by which seed orientations in stranded implants can be derived from the post-implant CT, and to use this to more accurately model the impact of seed anisotropy on the dose distribution. First, a plan reconstruction algorithm\textsuperscript{175} was used to identify strands in the post-implant CT. Then, a smooth curve was fit to the seed positions along each strand, respecting an inter-seed arc length equal to the strand-maintained spacing. The orientation of each seed was considered to be the tangent vector to the curve at the seed’s position. The 2D dose-calculation formalism was modified to account for uncertainty in orientation, and used to generate an improved estimate of the implanted dose distribution. This was compared to the 1D-derived distribution in a cohort of 30 patients.
3.2 Methods

3.2.1 Plan Reconstruction

Thirty day-0 post-implant CT studies, acquired as part of routine post-implant quality assurance, were analyzed in this study. Seed segmentation and plan reconstruction were performed on these scans by an automatic algorithm to localize the seeds and group them into strands, as described in Chapter 2. This can be done because plan reconstruction computes a correspondence between the planned and implanted positions of the seeds, from which strand assignments can be deduced. A consensus regarding the accuracy of the automatic reconstructions was reached by three independent observers, using the expected spacing between stranded seeds, strand depth and relative positioning, and number of seeds per strand as indicators.

3.2.2 Strand Fitting

It was assumed that seeds were constrained by the strand material, and remained tangent to the strand through the encountered ranges of implanted strand curvature. Each strand was modeled as a natural cubic spline. A cubic spline is a piecewise function of cubic polynomials defined between a set of fixed control points, and exhibits $C^0$, $C^1$ and $C^2$ continuity. This means that each piecewise section intersects at the fixed points, and their first and second derivatives at these points are equal. The natural cubic spline has null second derivatives at its boundaries and is unique in that it is the smooth function of minimum curvature that passes through the set of fixed points. It is thus a popular tool to model the bending of physical objects whose internal resistance favors minimum curvature. Natural cubic splines were fit to each strand using the seed centres as the fixed control points.

The probability density $P_{so}$ of seed orientations derived from the strand fitting procedure was described with a von Mises-Fisher distribution\(^{176}\), a spherical analogue of the normal distribution. The distribution’s parameters are the unit vector ($\mu$) and scalar concentration ($\kappa$), which play a role similar to the mean and variance in a normal distribution. For $\kappa = 0$ the density is uniform on the unit sphere, and collapses around $\mu$ as $\kappa$ increases. The von Mises-Fisher probability density function is shown in Eqn. (3.1), where $x = (x, y, z)$ is a unit vector parallel to the seed’s long axis in the CT frame.

$$P_{so}(\kappa, \mu, x) = \frac{\kappa}{4\pi \sinh(\kappa)} \exp(\kappa \mu^T x)$$ (3.1)

3.2.3 Effect of Seed Localization Uncertainty on Fit

Uncertainty in the segmented positions of the seeds can lead to a strand-fit for which the inter-seed spacing along the spline does not equal the planned spacing. An iterative optimization algorithm (Nelder-Mead simplex) was used to determine if a set of seed positions within a specified range of uncertainty existed for
which the spline fit resulted in a discrepancy of <5% between the planned and fit spacing. Seed positions were adjusted accordingly, and their orientations were then derived and used for 2D dosimetry. If the algorithm was unable to find such a fit, the reconstructed needle was reviewed. Occasionally, a pair of seeds in a strand appeared to be much closer than expected, and could not be fit within tolerance. Possible explanations for this will be discussed subsequently. Any pairs of seeds that could not be properly fit were treated using the 1D formalism.

Seed localization accuracy is finite. A number of factors contribute to this, including the geometry of the CT scanner, patient movement, internal movement of the radio-opaque marker with the seed, and the sophistication of the seed-finding software used to abstract seed centroids from the noisy images. The local post-implant pelvic CT imaging protocol calls for a slice spacing of 2.5 mm and a slice thickness of 3 mm for post-implant analysis, with an in-plane resolution of approximately 0.2 mm and. Seeds, which to a first approximation lie along the CT axis, may be evident on up to three slices. The seed finding software used in this thesis to determine the centroid of these blobs is typically accurate to a half-slice thickness, or 1.25 mm. These uncertainties were aggregated and modeled by assuming a 3D-Gaussian probability distribution for each seed centroid, with standard deviations of $\sigma_z = 0.5$ mm, and $\sigma_x = \sigma_y = 0.2$ mm. These values were chosen so that a distance of $2\sigma$ from the typical seed centroid corresponded to the edges of its blob artifact.

### 3.2.4 Spline Sensitivity Analysis

A sensitivity analysis was undertaken to assess the extent to which seed position uncertainty propagates through the fitting process to affect the calculated seed orientation. Four strands, ranging from three to six seeds long, were randomly selected from the cohort. This was complemented with a synthetic straight strand with four seeds. These strands were digitized into sets of seed coordinates, to which Gaussian zero-mean noise was applied to the positions in the CT coordinate system. Four different levels of noise were used, characterized by a standard deviation in each axis (see Table 3.1). In the CT frame, $x$ is left-positive, $y$ is posterior-positive, and $z$ is superior-positive. Azimuthal angles are positive in the clockwise direction from the $x$-axis. After applying noise at a given level, the strand fitting procedure described above was performed to search for a feasible fit. The error in the inclination ($\alpha$) and azimuth ($\beta$) from ground-truth were determined from these fits. Ten thousand histories were accumulated to study the distribution of the errors. These distributions defined the region over which anisotropy was integrated during dose calculations.
Table 3.1: Noise level parameters, expressed as the standard deviations in each CT axis for zero-mean Gaussian noise.

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<thead>
<tr>
<th>Level</th>
<th>$\sigma_x$ (mm)</th>
<th>$\sigma_y$ (mm)</th>
<th>$\sigma_z$ (mm)</th>
<th>$\sqrt{\sigma_x^2 + \sigma_y^2 + \sigma_z^2}$</th>
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</thead>
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<td>Level 1 (lowest)</td>
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<td>0.1</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td>Level 2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.5</td>
<td>0.52</td>
</tr>
<tr>
<td>Level 3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.5</td>
<td>0.57</td>
</tr>
<tr>
<td>Level 4 (highest)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.75</td>
<td>0.81</td>
</tr>
</tbody>
</table>

3.2.5 Phantom Evaluation

A phantom experiment was conducted to investigate the accuracy with which the fitting process reproduced strand pose from seed positions. Two grooves, one cubic and one quadratic, were etched into sheets of Solid Water® (Gammex, Middleton, WI) as per Eqns. (3.2a, 3.2b). Dummy strands were embedded into these grooves, and the sheets placed into a stack and CT scanned. The images were then imported into the Plan Reconstruction software, in which seed positions were segmented, and the two curves reconstructed using the fitting procedure as described. The result was compared to the ground-truth to evaluate the goodness of fit over the entire strand. The maximum and root-mean-square errors were calculated, as well as $R^2$ coefficients of determination.

$$y_{\text{quad}} = 0.01(x - 10)^2 + 10$$  \hspace{1cm} (3.2a)

$$y_{\text{cubic}} = -0.145\left(\frac{(x - 10)}{10}\right)^3 + 1.876\left(\frac{(x - 10)}{10}\right)^2 + 5$$  \hspace{1cm} (3.2b)

3.2.6 Dose Calculations Using the 2D Formalism

For each patient in the cohort, structure contours were delineated by the oncologist and extracted from the DICOM CT files exported by the planning software. In-house dose calculation software was written to calculate and compare the dose distributions. The dose-voxel grid spacing was set to 1 mm in the $x$ and $y$ axes, and 2.5 mm in the $z$ direction.

The longitudinal axis of each seed was found by computing the tangent to the spline that was fitted to the strand at the seed’s centroid. A small number of loose seeds, which are occasionally used to supplement the plan at the discretion of the implanting physician, were treated using the 1D formalism. The TG-43 parameters used in this study for the 6711 source model were derived by Monte Carlo techniques as described by Taylor et al.\textsuperscript{177}. These were chosen over the TG-43 consensus values\textsuperscript{82} because of the resolution and range of the 2D anisotropy tables. Taylor et al.’s functional fit to the radial dose function was used, and anisotropy data interpolated linearly. Points which fell outside the range of the tables were treated as if they were at the boundaries.
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Eqn. (3.3) describes the expected dose rate to a point at \((r, \theta)\) in the TG-43 coordinate system, where the fit-derived longitudinal axis of the seed lies along the \(z\)-axis. For a fitting process with finite accuracy, the true orientation of the seed with respect to the fit orientation is described by a distribution parameterized by inclination \(\alpha\) and azimuth \(\beta\). The parameter \(\gamma\) is defined as the polar angle to the point \((r, \theta, \phi)\) from the true longitudinal axis of the seed. Note that in this analysis, \(\gamma\) parameterizes the TG-43 anisotropy and geometric functions, rather than \(\theta\). The trigonometric relationship between \(\gamma\), \(\theta\), \(\phi\), \(\alpha\), and \(\beta\) is shown in Eqn. (3.4), and an illustration of the geometry is shown in Figure 3.1.

The density of \(\gamma\) is denoted by \(P_{\text{fit}}(\gamma, \theta)\), and is characteristic of the accuracy of the fitting procedure. A numerical histogram-based estimate of this distribution was made in order to evaluate Eqn. (3.3). This used distributions of \(P(\alpha)\) and \(P(\beta)\) derived from the sensitivity analysis described in Section 3.2.4. Thus, the 2D dose from each seed is an average over the distribution of possible orientations that can be calculated by fitting strands to imprecisely segmented seeds. Note that the equation assumes the proper modular transformation of \(\gamma > 90 \rightarrow 180 - \gamma\).

\[
E[\dot{D}(r, \theta)] = \frac{S_k \Lambda g(r)}{G_L(r_0, \theta_0)} \int_{\gamma=0}^{90} F(r, \gamma) G_L(r, \gamma) P_{\text{fit}}(\gamma, \theta) d\gamma \tag{3.3}
\]

In Eqn. (3.3), variable naming is consistent with TG-43, where \(F\) is the anisotropy function, \(G_L\) is the geometry function for a line source, \(S_k\) is the air-kerma strength, \(\Lambda\) is the dose rate constant, and \(g(r)\) is the radial dose function. The reference distance and reference angle \(r_0\) and \(\theta_0\) are 1 cm and 90° respectively. Eqn. (3.3) characterizes the continuum between the 1D and 2D formalisms, representing the situation where seed orientation is known to within a certain degree of uncertainty. If \(P_{\text{fit}}(\gamma, \theta)\) is taken to be \(\sin(\theta)\),
between 0° and 90°, and zero elsewhere, the equation reduces to the TG-43 1D expression. If $P_{in}(\gamma, \theta)$ is taken to be $\delta(\theta - \gamma)$, where $\delta$ is the Dirac-delta function, it reduces to the 2D formalism.

$$\gamma = \cos^{-1}\left( \cos \alpha \cos \theta + \sin \alpha \left( \cos \beta \sin \theta \cos \phi + \sin \beta \sin \theta \sin \phi \right) \right) \quad (3.4)$$

Two different estimates of $P_{in}(\gamma, \theta)$ were made, one for the seeds at the ends of the strands (‘terminal seeds’), and one for the remainder (‘central seeds’). The reason for this was that the former was noted to have a consistently larger variance during preliminary testing. In addition, since the assumption that $P(\beta)$ is uniform only has a minor impact on $P_{in}(\gamma, \theta)$, this simplification was adopted for computational reasons.

All 2D dose distributions calculated in this study were calculated using Eqn. (3.3) rather than the standard TG-43 2D formalism, which does not average over orientation uncertainty. To make this distinction clear, dose calculations reported herein are described as ‘2D-weighted’.

### 3.2.7 Evaluation

For each of the 30 patients, the day-0 post-implant dose distribution was calculated using both the 1D and 2D-weighted formalisms. Both primary and secondary dose parameters as specified by TG-137 were recorded for each structure. For the prostate (CTV) these were the D90, D100, V100, V150, and V200. For the prostatic urethra, these were the UD10, UV150, UD0.1cc, UD30, and UD5, and for the rectum, the RV100, RD0.1cc and RD2cc. In addition, the median absolute difference in the dose to the prostate, and difference in total volume at the prescription dose level as a percentage of prostate volume were also recorded. The mean of the paired differences in these endpoints between the 1D and 2D-weighted dose distributions were analyzed using a paired Student’s t-test at a significance level of 0.05.

### 3.3 Results

#### 3.3.1 Phantom Validation

The spline fits to the two embedded strands were accurate to within 2° over the length of the strand. The coefficient of determination $R^2$ was 0.999 for the quadratic curve and 0.996 for the cubic curve. In both cases, the root-mean-square (RMS) errors were $< 0.3$ mm. The maximum absolute error between the fitted curves and the grooves was 0.5 mm. These errors were considered to be within the range of setup uncertainty. Reducing the number of seeds used for fitting increased the maximum absolute error. For a three seed fit to the cubic curve in the region near the end of the seed train ($80 < x < 100$ mm in Figure 3.2), this reached a maximum of 0.7 mm.
Figure 3.2: Phantom validation of the fitting procedure. Strands were embedded into grooves based on (a) cubic and (b) quadratic functions, which were etched into sheets of Solid Water® (inset, not to scale). The phantom was imaged using CT and the seeds segmented and fit using the spline algorithm. For both cases, the RMS error was < 0.3 mm, the maximum absolute error was 0.5 mm, and the maximum error in the curve tangent (seed orientation) was 2°.

3.3.2 Sensitivity Simulation

Terminal seeds were consistently more sensitive to segmentation uncertainty than central seeds, with mean errors in inclination (mean $\alpha$) an average of 1.9 times larger. The errors in fitted position and orientation for four different applied noise levels are presented in Table 3.2. Errors increased in proportion to noise, with relatively greater sensitivity to noise in the transverse plane. As described in Section 3.2.6, estimates of the distributions $P(\alpha)$ and $P(\beta)$ were necessary for dose calculations. The ones used for this purpose were those derived using the simulation parameters corresponding to the assumed uncertainty in seed centroids given in Section 3.2.3. Plots of these densities are shown in Figure 3.3 and Figure 3.4, respectively, to illustrate the difference between the terminal and central seeds. The insensitivity of $P_{\text{true}}(\gamma, \theta)$ to the assumption that uncertainty in the azimuth of the fit is symmetric around the z-axis (i.e. $P(\beta)$ is uniform) is illustrated in Figure 3.5 at a variety of different measurement point inclinations.
### Table 3.2: Errors in sensitivity analysis.

A test-set of 5 reconstructed strands had simulated noise applied and the effects on the computed position and orientation of their seeds were studied. Fitted error in seed position and polar orientation ($\alpha$) are reported for each noise level. Values are means, plus/minus one standard deviation for the orientations. Maximum values are displayed in parentheses.

<table>
<thead>
<tr>
<th>Noise Level</th>
<th>Applied error (mm)</th>
<th>Error in fitted position (mm)</th>
<th>Error in fit inclination $\alpha$ (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Terminal</td>
<td>Central</td>
</tr>
<tr>
<td>1</td>
<td>0.28</td>
<td>0.2</td>
<td>1.2±1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.7)</td>
<td>(6.01)</td>
</tr>
<tr>
<td>2</td>
<td>0.52</td>
<td>0.3</td>
<td>1.9±2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.3)</td>
<td>(10.8)</td>
</tr>
<tr>
<td>3</td>
<td>0.57</td>
<td>0.4</td>
<td>2.3±2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.4)</td>
<td>(12.0)</td>
</tr>
<tr>
<td>4</td>
<td>0.81</td>
<td>0.6</td>
<td>3.1±3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.2)</td>
<td>(23.8)</td>
</tr>
</tbody>
</table>

Figure 3.3: The sensitivity simulation-derived probability density of the seed inclination error $\alpha$ for four different levels of applied noise in (a) central and (b) terminal seeds. Noise levels are in increasing order of magnitude.
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Figure 3.4: The sensitivity simulation-derived probability density of the seed azimuth error $\beta$ for four different levels of applied noise in (a) central and (b) terminal seeds. Noise levels are in increasing order of magnitude.

3.3.3 Strand Orientation

Of the 761 strands evaluated in this study, only five (0.66%) did not accommodate a fit that respected the seed spacing to within 5%. Four of these situations arose in the most cranial seeds of anteriorly deposited strands, which we hypothesize was due to the extracapsular portion of the strand being deflected caudally, either by the bladder or some other shearing force on the surface of the gland. This resulted in a pronounced kink, and the orientation estimate for these seeds was noticeably less accurate. In the fifth case the strand was located in the lateral aspect of the gland, and the cause of the apparent compression between seeds is unclear. Seeds which could not be properly fit in these cases were always too close to each other, suggesting that the spline segment connecting those seeds lacked sufficient curvature. As no additional data was available to further clarify this issue, the offending seeds in these strands were treated with the 1D formalism in both the 1D and 2D-weighted arms.

Statistics on the orientation of seeds within each implant were compiled to test the validity of the assumption that strands lie predominantly along the longitudinal ($z$) axis of the scanner. The average inclination of each seed from this axis was $21 \pm 10$ degrees, with an average azimuth of $-81 \pm 57$ degrees. This corresponds to a mean orientation that lies at an anterior pitch from the coronal plane: $\mu_x = -0.019$, $\mu_y = -0.31$, and $\mu_z = -0.95$. 
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Figure 3.5: The probability densities of the fitted seed inclination (in deg\(^{-1}\)) plotted for measurement points every 10 degrees of inclination for (a) central seeds and (b) terminal seeds. Multiple densities are overlaid on a single plot for compactness; each is centred at the measurement inclination (\(\theta\)) and falls to zero on either side. The dependence of these plots on the azimuth (\(\phi\)) of the measurement point can be seen when comparing the densities of points at \(\phi = 0\) and \(\phi = 90\) using the probability density of the fitted seed azimuth \(P(\beta)\) derived from sensitivity-simulations. Making the assumption that \(P(\beta)\) is uniform splits the difference in the extremes, and eliminates the dependence of the measurement azimuth (in the seed (TG-43) frame).

Figure 3.6: Probability density (in deg\(^{-1}\)) of the (a) inclination and (b) azimuth for stranded seeds in the CT coordinate system. Histogram bars are the raw counts in bins of 5\(^\circ\), and solid curves represent the orientation probability density \(P_{SO}\). The probability density assumed by the 1D formalism is shown for comparison. (c) In this image, \(P_{SO}\) is projected onto the unit sphere using color intensity to highlight regions of high density. The grid interval is 10\(^\circ\), and the directions of the CT axes are labeled (A – anterior, P – posterior, R – right, L – left, I – inferior, S – superior). Most seeds exhibit an approximately 20\(^\circ\) pitch from the coronal plane toward the anterior of the patient.
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The maximum-likelihood value of the von Mises-Fisher concentration parameter was \( \kappa = 30.1 \). The quality of fit with respect to the raw histograms can be seen in Figure 3.6. The prime symbols are used to denote angles measured in the CT coordinate system, where the \( z \) axis is cranial superior, and the \( x \) axis is left-lateral superior. An illustration showing the projection of the probability density onto the unit sphere is also included.

### 3.3.4 Dosimetric Impact of 2D Dose Calculation

The application of the 2D-weighted calculation resulted in statistically significant changes to the TG-137 recommended DVH parameters, which are shown on Table 3.3. From a clinical perspective, however, the differences were small and unlikely to be of concern. The use of 2D-weighted dosimetry increased apparent coverage at the prescription dose level, whereas high dose volumes contracted. The median absolute voxel-to-voxel dose difference within the prostate between the two dose distributions across the cohort was 3.4 Gy (range 2.5 - 4.2 Gy). Volumes which differed by more than 7.2 Gy and 14.4 Gy (5% and 10% of the prescription dose respectively) were mostly confined to the vicinity of the seeds, although some projection of the 5% difference volume was also evident on the superior and inferior aspects of the seed cloud (see Figure 3.7a). The 1D dose distribution universally underestimated V100 and V90 and overestimated V150 and V200. D90 was also consistently underestimated by a mean of 2.3 Gy (range 0.6 Gy to 3.8 Gy).

Qualitatively, anteromedial gaps in the prescription isodose cloud were often observed to close when 2D-weighted dosimetry was used. This was generally accompanied by defects in the cloud between seeds at the superior and inferior aspects of the implant (see Figure 3.7b). These phenomena were a result of both strand alignment, and the non-uniformity of strand density in the BCCA planning style. A consequence of shaping the V150 away from the anteromedial region in planning is that post-implant dose there is often close to the prescription threshold. This makes reported coverage at this level sensitive to small changes in the dose calculation.

Urethral and rectal doses in the cohort were generally low. Doses to these structures were typically underestimated by the 1D formalism. This is consistent with the roughly parallel alignment of these structures with the strands. As with the prostate, differences in DVH parameters were minor. The cohort maximum increase for the urethra when 2D-weighted dosimetry was performed was 6.7 Gy with respect to UD30, and 4.5 Gy for the rectum with respect to RD0.1cc.
Chapter 3 - Determining the Orientation of Implanted Seeds

<table>
<thead>
<tr>
<th></th>
<th>Cohort Mean 1D</th>
<th>Cohort Mean 2D</th>
<th>Mean paired difference (2D-1D)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V90 (%)</td>
<td>95.3 ± 3.6</td>
<td>96.1 ± 3.2</td>
<td>0.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>V100 (%)</td>
<td>90.7 ± 5.7</td>
<td>91.8 ± 5.3</td>
<td>1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>V150 (%)</td>
<td>45.1 ± 9.3</td>
<td>43.5 ± 9.7</td>
<td>-1.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>V200 (%)</td>
<td>14.6 ± 4.3</td>
<td>13.3 ± 3.8</td>
<td>-1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D90 (Gy)</td>
<td>147.7 ± 10.0</td>
<td>150.0 ± 9.8</td>
<td>2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D100 (Gy)</td>
<td>87.1 ± 12.0</td>
<td>88.9 ± 12.6</td>
<td>1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Prostatic Urethra</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UD30 (Gy)</td>
<td>163.7 ± 18.4</td>
<td>167.5 ± 18.3</td>
<td>3.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>UD10 (Gy)</td>
<td>177.8 ± 21.5</td>
<td>181.4 ± 21.1</td>
<td>3.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>UD5 (Gy)</td>
<td>184.2 ± 24.7</td>
<td>187.2 ± 23.4</td>
<td>3.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>UD0.1cc (Gy)</td>
<td>183.7 ± 28.0</td>
<td>186.8 ± 26.8</td>
<td>3.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV100 (cc)</td>
<td>0.5 ± 0.6</td>
<td>0.6 ± 0.7</td>
<td>0.1</td>
<td>0.004</td>
</tr>
<tr>
<td>RD2cc (Gy)</td>
<td>99.6 ± 22.7</td>
<td>101.6 ± 22.6</td>
<td>1.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RD0.1cc (Gy)</td>
<td>161.1 ± 37.5</td>
<td>161.7 ± 35.8</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Rx isodose volume</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>(as % of prostate volume)</td>
<td>163.6 ± 26.1</td>
<td>164.0 ± 26.3</td>
<td>0.4</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 3.3: Cohort means and patient-controlled differences in selected dose metrics, comparing the 1D and 2D-weighted dose calculation methods. Listed p-values are for t-tests of the respective mean paired difference from zero.
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Figure 3.7: (a) Volumes with an absolute difference between 1D and 2D-weighted dose distributions of greater than 7.2 Gy (5% of prescription) (left/blue) and 14.4 Gy (10% of prescription) (right/orange). (b) 1D (left) and 2D (right) prescription isodose surfaces for one patient. The 1D formalism tends to overestimate dose margins at the superior and inferior aspects, and underestimate dose margins at the lateral boundaries and in the medial regions.

3.4 Discussion

The results herein are consistent with those of previous studies of seed anisotropy, which have reported only small differences in total dose due to variations in seed orientation, at least within the TG-43 formalism. Lindsay et al. compared 1D and 2D dose distributions for four source models, looking at the size of the volumes which changed by more than 10% of the D90 in nine post-implants. For the model 6711 seed, they found a mean variation of 8% (range 2-24%) in this measure. Chibani et al. compared three dose distributions which cumulatively included the effects of anisotropy and inter-seed attenuation, and reported a difference in V100, V150 and V200 of less than one percent. They concluded that the effect of inter-seed attenuation played a larger role than anisotropy in these differences. However, neither of these studies involved measuring actual seed orientations. Rather, both assumed that implanted seeds were either randomly oriented, or that they were collinear with the CT axis. Both studies also analyzed only a very small number of patients.

An empirical determination of the probability density of loose seed orientations was derived from plane film images by Corbett et al. They used this estimate to construct a ‘weighted anisotropy function’ to account for the tendency of seeds to be distributed along the needle axis. The dose distributions resulting
from this function were compared to those in which the seeds were assumed to be straight or randomly oriented. This group found that prostate V100 was largely invariant between dose calculation methods, whereas the 1D calculation marginally overestimated V150 and V200.

Corbett et al.’s study differs from the present one in how seed orientations were defined. The orientation of each seed in their study was assigned an identical probability density with respect to the patient, over which seed anisotropy was averaged. In essence, uncertainty in the orientation of each seed was regarded as a property of the variance in seed orientation with respect to a fixed axis.

In our work, the analogous density for stranded seed orientations is represented by the von Mises-Fisher distribution $P_{\kappa}(\kappa, \mu, x)$. However, this was not the distribution over which orientation was averaged for dose calculations. Instead, the orientation of each seed was individually determined, and anisotropy averaged over $P_{\kappa}(\gamma, \theta)$, which is defined with respect to the seed coordinate system. This distribution is a property of the accuracy of the fitting process, not the variance in seed orientations with respect to the patient.

The main aim of this study was to clarify any systematic errors that may be associated with using the 1D formalism, which many clinics use, to report on stranded-seed implants. Our results echo those of previous investigators. In general, the dosimetric impact of fluence anisotropy in stranded 6711 seeds on prostate dosimetry is minor. As anisotropy in the 6711 is slightly greater than in most other I-125 models (http://vali.physics.carleton.ca/clrp/seed_database/I125/), it is unlikely that most centres using I-125 will see more extreme differences than those found herein.

Dose-volume endpoints differed by approximately 2% in comparison to the 1D dose calculation. However, as these metrics tend to mask the effect of phenomena such as anisotropy, which causes geometrical redistributions of dose, voxel-by-voxel differences were also examined. These too were of minimal clinical significance. Discrepancies at the 5% and 10% of prescription level were found to lie predominantly in the near vicinity of the seeds. It seems unlikely that the efficacy of prostate implants from the perspective of clinical outcomes will be traceable back to small redistributions of dose that are presumably already above the level sufficient for ablation. Even comparatively gross differences in dosimetric parameters such as D90 at the BCCA have failed to predict for biochemical relapse\textsuperscript{117}, which calls into question the sensitivity, specificity, and generality of such whole-prostate dosimetric quantifiers in characterizing effective implants\textsuperscript{180}. Furthermore, a clear distinction should be drawn between real errors in computed dose, such as when anisotropy or medium heterogeneity is ignored, and the uncertainty that arises from other sources, such as variability in contouring. That the latter is considerable and obfuscates the results of QA and outcomes analysis is unfortunate, but it should not justify neglecting dosimetric errors which are perceived to be undetectable by the precision of current methodologies. Dosimetric accuracy should be striven for

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whenever feasible. Improvements in imaging standards\textsuperscript{100,181,182,183} and the increasing interest in brachytherapy as a focal therapy\textsuperscript{184,185} argue for continuing to advance post-implant dosimetric accuracy. The accuracy of the seed orientations derived in this study depends on the spline-fitting process to adequately reproduce the strand path. In phantom, the discrepancy between ground-truth and the fit was $< 2^\circ$, a substantial reduction in uncertainty compared to the assumption that the orientations were uniformly random. However, the full range of strand trajectories that occur in soft-tissue implants may not be completely modeled by natural cubic splines. In some regions of the implant, this limitation may dominate seed localization error as the principal contributor to orientation uncertainty. Strand trajectories depend on a complex interplay of needle-tissue interactions. Both patient-specific factors such as tissue stiffness and organ configuration, as well as procedure-specific factors such as needle gauge, bevel, and insertion force and velocity play a role\textsuperscript{186,187,188,189}. The ideal strand-fitting function would be derived from physical models developed from these investigations, but so far such models depend on detailed anatomical data which remains difficult to reliably acquire.

In this study, the positions of control points (seeds) were manipulated within a specified tolerance in order to find splines which respected the suture-imposed seed spacing. This may appear an oblique way of enforcing spacing constraints. Yet, the seemingly more direct method of searching for a minimal energy path of constrained length between a set of fixed control points is difficult. Algorithms which find such paths have been proposed, but require tangents to be provided at control points\textsuperscript{190,191}, which presumes the answer that is sought. Despite the limitations of our model, the estimates of seed orientation made herein for the purposes of evaluating 2D dosimetry are a refinement on those of previous studies, and the method is fast and clinically feasible.

This study focused on day-0 dosimetric outcomes, as is the protocol at the BCCA. It must be recognized, however, that post-implant dosimetry is more commonly carried out after an interval of approximately one month (“day 30”), when the effects of edema have largely resolved\textsuperscript{97,98,99,113}. At this time, seed orientation is typically observed to have become more random than on day 0. Our previous experience\textsuperscript{107} in plan reconstruction at day 30 also suggests that intra-strand seed spacing becomes more variable. These factors are likely to exacerbate the model limitations identified in the previous paragraphs. Nevertheless, it should be possible to address some of the problems by modifying $P_{\text{fit}}$ to reflect the increase. Determining appropriate distributions for this task will require further research. However, in considering the utility of further investigations of this nature purely for assessing dosimetric differences between the 1D and 2D-weighted formalisms, it should be recognized that any small differences seen for the less randomly oriented day 0 stranded implants used in this study will only become even smaller at day 30. Of course, this does not preclude extending the methodology to day 30 for other purposes.
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The final noteworthy limitation of this study regards the determination of the distribution of seed orientations with respect to the patient. The generality of von Mises-Fisher distribution parameters derived from this cohort is diminished by the fact that the angle of the ultrasound probe for each patient was not recorded. Consequently, the extent to which the distribution in seed orientation could be accounted for by variations in probe angle could not be determined. A similar limitation was present in Corbett et al.’s study, which is, to our knowledge, the only other study to determine seed orientation distributions from measurement. Future investigators should take care not to repeat this oversight. At this institution, the probe angle is selected so as to achieve good contact with the prostate, and is usually between zero and five degrees, with an upper limit of approximately 15 degrees. The applicability of our estimate of mean strand orientation to the broader community will therefore depend on the similarities in patient setup protocols.

At our centre, plan reconstruction is performed routinely to validate seed segmentation. Like a jigsaw puzzle with missing or additional tiles, false positive or negative seed identifications are easier to discern when the segmented seeds are required to reconstitute a coherent reconstruction. This independently motivates utilization of the strand reconstruction procedure, which is the most time-consuming aspect of the methodology described in this paper. The additional overhead associated with strand-fitting is approximately eight seconds. However, the increase in computational complexity when 2D-weighted dosimetry is used is not insignificant, as a large number of vector rotations are necessary. Parallelization may be exploited to make the dose calculation time reasonable. The prototype MATLAB code used in this study took approximately 1s per 100 seeds at a 1x1x2.5 mm³ voxel resolution. The calculations were performed on an Intel 3.0 GHz Core2 CPU, with 4 GB of memory and an NVIDIA GTX 260 GPU.

3.5 Conclusions

Using a novel strand-fitting procedure to determine seed orientations, this study finds that the alignment of strands along their axes of implant does not meaningfully affect the primary and secondary dose metrics recommended by the ABS and AAPM to evaluate implant quality, at least for the 6711 source model. At day-0, the TG-43 1D calculation agreed with the 2D calculation to within ~2% for most dosimetric endpoints. This is likely to be sufficiently accurate for the routine quality assurance of stranded implants, and to compare loose and stranded seed implant quality without substantial bias. However, seed orientations consistently exhibited a mean anterior pitch of 21 ± 10° degrees. Depending on institutional protocols for patient setup, the common assumption that seeds are aligned with the CT scanner axis may be inaccurate. The accuracy of the fitting method used in this work may also be valuable to investigators considering the translation of this technique to other purposes, such as making quantitative measurements of needle deflection or prostate deformation for path planning.
Chapter 4 – The post-implant dynamics of stranded seeds

4 The Post-implant Dynamics of Stranded Seeds

4.1 Introduction

Significant prostate edema occurs after PIPB, induced by trauma from the needles used to deposit the radioactive seeds. Edema is believed to peak shortly after the implant, taking between one and three months to resolve. The volume changes that occur during this interval affect the relative positions of the seeds implanted into the gland. Ignoring its effects can lead to errors in the post-implant estimation of the dose distribution. The magnitude of the error depends on the rate at which edema subsides and the timing of the post-implant evaluation. In an effort to compensate for such errors, a number of ‘dynamic’ models have been proposed to incorporate the trajectory of edema into the dose calculation.

The dosimetric uncertainty that occurs during the resolution of edema also has a component that may be considered separate from the edema effects themselves. The fixity of seeds within the prostate tissue may be compromised, resulting in distant migration via embolism, ejaculation, or urinary routes. In current dynamic models, non-migrating seeds are generally assumed to move in synchrony with their local environment as edema resolves. To date, studies supporting this correlation between seed displacement and edema have largely relied on calculated dose distributions as a surrogate for direct temporal tracking of seed positions. Post-implant time trends in dosimetry have widely been reported as consistent with a contraction of the implant and prostate volume. However, quantitative measures of the degree of synchrony between seed positions and tissue as edema resolves remain unclear. The main purpose of this study was to compare the theoretical expectations of seed dynamics against clinical data.

In addition to the above objective, the patterns of distant seed migration were also investigated. This work is novel in that the origin of each migrating seed was determined via plan reconstruction. This enabled the assessment of the situational factors that may have influenced each seed’s risk of migration, rather than simply characterizing overall seed loss.
4.2 Methods

4.2.1 Study Cohort

Data for this study was acquired from the routine post-implant data of 28 patients treated with PIPB at the Vancouver Centre from late-2010 to mid-2011, for whom both day-0 and day-30 CT were available as part of an independent quality assurance study. Patient characteristics are summarized in Table 4.1. All day-0 CT scans were acquired within two hours of the implant, after the patient was released from the OR recovery room. Note that for convenience the second scans are labeled as nominally ‘day-30’, although there were minor timing variations in the cohort due to scheduling (Mean=29±3.2d, range 21-35d). However, where appropriate in edema calculations, patient-specific intervals between scans (to the nearest day precision) were used.

In all but one case, MRI scans were also acquired at approximately day-30. Six patients had adjuvant hormone therapy, 5 for ≤6 months. One high-risk patient had been on hormones for a year prior to implant. MR-CT fusions, were used to investigate anatomical causes of migration, but since MR was not available at day-0, all contouring for the purposes of evaluating dosimetry was performed on CT to limit any systematic bias in volume estimation due to imaging modality. Image fusions and dose calculations were performed using Variseed 8.02 (Varian Medical Systems, Palo Alto, CA).

<table>
<thead>
<tr>
<th>Pretreatment characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Median (range) 65 (54 – 81)</td>
</tr>
<tr>
<td></td>
<td>Stage T1a / T1c / T2a / T2b / T2c 1 / 19 / 3 / 2 / 3</td>
</tr>
<tr>
<td></td>
<td>Gleason Score 6 / 7 / 8 4 / 23 / 1</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>Median (range) 6.6 (1.3 – 29)</td>
</tr>
<tr>
<td>Prostate Volume (cm³)</td>
<td>Median (range) 45.9 (22.5 – 71)</td>
</tr>
<tr>
<td>+Hormones</td>
<td>7</td>
</tr>
<tr>
<td>Needles (#)</td>
<td>Median (range) 26 (21 – 32)</td>
</tr>
<tr>
<td>Seeds (#)</td>
<td>Median (range) 126 (95 – 161)</td>
</tr>
</tbody>
</table>

Table 4.1 : Pretreatment characteristics of the study cohort
Chapter 4 – The post-implant dynamics of stranded seeds

4.2.2 Plan Reconstruction

The principal novelty of this work is that the effects of edema on seed displacement and migration are evaluated using individual seeds matched between imaging time-points. This was accomplished using the plan reconstruction technique described in Chapter 2. A total of 3628 seeds were matched and analyzed herein.

This study required plan reconstruction at day-30. Although day-0 reconstructions are unambiguous in the majority of cases, day-30 reconstructions are more challenging, as inter-seed spacing is no longer as robust a criterion for assigning seeds to strands. Performing reconstructions of day-30 seed clouds with only the pre-plan for guidance is usually impractical due to the distorting influences of migration and edema in addition to the existing delivery uncertainties present in the day-0 seed distribution. However, by first reconstructing the day-0 plans, and matching seeds in the day-30 distributions with respect to these rather than the preplan, delivery uncertainties are controlled for, and accurate reconstructions at day-30 are thus typically achievable. Since there is no ground-truth, each reconstruction was reviewed by three independent observers to minimize the opportunity for errors.

4.2.3 Day-0 to Day-30 Implant Registration

The day-0 and day-30 seed clouds were initially registered by aligning the average position of the implants at day-0 and day-30. During the course of the study, it became apparent that there were often pronounced differences in the pose of the strands after registration, suggesting that the prostate itself was misaligned. This was attributed to variable rectal or bladder filling, edema of the genitourinary diaphragm, and slight differences in patient setup between the two scans. These effects were assumed to displace the whole gland systematically, and a rigid pose correction was performed to bring the average trajectory of the strands at day-0 into alignment with the strands at day-30.

As the scope of the term ‘migration’ in the literature is somewhat inconsistent, the following terminology has been adopted in this chapter: Displacements are the vector differences in position between seeds in the registered day-0 and day-30 frames. Distant migrations refer to seeds that could not be found in the scan volume at day-30. Seeds which had appeared to separate from their strand were classified as local migrations. The definition for local migration was when the distance between a seed and its intra-strand neighbour increased by more than 1 cm relative to their separation at day-0.

Importantly, seeds classified as migratory (local or distant) were excluded from the subsequent edema model evaluation. The displacements of such seeds were clearly independent of the dynamics of the underlying prostate tissue. The focus where distant migrations were encountered was to review the CT or MRI scans for proximal risk factors, such as implantation near the bladder wall or urethra.
4.2.4 Contraction Models for Edema-Induced Seed Dynamics

Individual stranded seeds were tracked between day-0 and day-30 on post-implant CTs, and the discrepancies in displacement between these observations and those predicted by existing models for prostate contraction were analyzed. The distance-to-agreement (DTA) is defined as the distance between a seed at day-0, or after the application of an edema correcting model to the day-0 data, from its position at day-30. The baseline DTA was defined as the DTA before any edema correction. In the ideal situation in which the seed localization and registration are perfect, the prostate behaves in accordance with an edema model, and the displacements of seeds occur in perfect synchrony with the resolution of edema, the DTA will be small. Deviations from this indicate that at least one of these criteria has been violated. One limiting factor in the accuracy of sequential seed tracking is the potential for the radio-opaque silver rod to move within the seed capsule itself\(^{201}\). This phenomenon may result in DTA of approximately 1 mm even if the capsule itself displaces as predicted by the edema model.

Mathematical models for edema describe the position of locations in the prostate as a function of time and the magnitude of edema. In order to apply the edema models to the day-0 data, an estimate of the edema magnitude (\(\Delta\)) was necessary. Recall from Chapter 1 that the edema magnitude is the maximum increase in prostate volume after implant, with respect to some non-edematous reference volume. In this study, two different methods for estimating patient-specific edema were used to study the impact of this choice on the results. In both cases it was assumed that the maximum volume was reached at day-0.

The first method used the ratio of the day-0 CT to pre-implant TRUS volume. This expression is shown in Eqn. (4.1a), where \(V_{\text{max}}\) and \(V_{\text{pre}}\) are the volumes measured on day-0 CT and TRUS respectively. The results derived from this value are of interest because it is easily computed for all patients at day-0, when edema-corrected dosimetric estimates at later time-points are most salient. However, this estimate is likely to be inaccurate for established reasons, such as systematic differences in volume measurements derived between CT and TRUS\(^{101,202}\), and the effects of contouring variability\(^{99}\). To control for this, all edema models were also run using an estimate of the edema magnitude derived from the ratio of the mean seed radii at day-0 and day-30, as originally performed by Waterman et al.\(^{98,113,196}\). This expression is shown in Eqn. (4.1b), in which \(r(0)\) and \(r(30)\) are the mean radial distances of the seeds. All radii in this study are measured from the centre of seed mass, the average position of all the seeds in an implant.

\[
\Delta_{\text{CT/TRUS}} = \frac{V_{\text{max}}}{V_{\text{pre}}} - 1 \quad \text{(4.1a)}
\]

\[
\Delta' = \left( \frac{r(0)}{r(30)} \right)^3 - 1 \quad \text{(4.1b)}
\]

In addition to simulating these patient-specific values, a range of edema magnitudes at 0.1 unit intervals between 0.1 and 0.8 were also considered.
The values of edema magnitude were fed into two previously published models which have been used to describe edema-induced volume changes. The first model is the isotropic-exponential (IE) contraction proposed by Waterman et al.\textsuperscript{98}. This model gives the position of a point at time $t$ with respect to the centre of the implant as:

$$r^{iso}(t) = r(0) \left( \frac{1 + \Delta \exp(-\lambda_e t)}{1 + \Delta} \right)^{1/3}$$ \hspace{1cm} (4.2)

where $r(t)$ in Eqn. (4.2) is the position of the seed from the centre of the prostate at time $t$, and $\lambda_e$ is the edema half-life.

The second model, described by Eqn. (4.3), is the anisotropic-linear (AL) contraction proposed by Monajemi et al.\textsuperscript{109}, in which the proportion of contraction along each of the CT axes is variable:

$$r^{aniso}_i(t) = \begin{cases} r'_i(0) \left( \frac{1 + \Delta(1-t/T_E)}{1 + \Delta} \right)^{\alpha_i} & t \leq T_E \\ r'_i(0) \left( \frac{1}{1 + \Delta} \right)^{\alpha_i} & t > T_E \end{cases} \hspace{1cm} (4.3)$$

The subscript $i \in \{x, y, z\}$ indicates the axis along which $r^{aniso}_i$ is measured, so that $r^{aniso}(t) = (r^{aniso}_x(t), r^{aniso}_y(t), r^{aniso}_z(t))$. For the sake of comparison with the original study, the values for $\alpha$ used therein were adopted: $\alpha_x = 0$, and $\alpha_y = \alpha_z = 1/2$. This corresponds to a gland contracting at equal rates in the anterior-posterior and superior-inferior directions, with static lateral dimensions.

### 4.2.5 Total Systematic Displacement

Any discrepancies between model-predicted seed displacements and those measured do not strictly imply that seeds are shifting with respect to the prostate. It is equally possible that the model or its parameters are incorrect, or not generally applicable. It was therefore desirable to construct a control, to distinguish whether systematic patterns in seed displacements were occurring which were simply not captured by the model. To accomplish this, a transformation based on thin-plate splines (TPS)\textsuperscript{203,204} was fitted to the data. As this transform is non-rigid and independent of a presumed anatomical mechanism, it was considered to be more likely to discern any latent systematic patterns in seed displacements. If such patterns exist, they may indicate the need for a more sophisticated approach to modeling the dynamics of the prostate gland.

The TPS transform minimizes the total amount of energy required to bring a set of landmarks into coincidence. The definition of the energy is based on a physical analog: the effort that might be required to
bend a set of thin sheets on which one set of landmarks lie, until they are coincident with the second set. In this study, these landmarks were based on statistical descriptors of subpopulations of seeds clustered at different points in the implant.

Recall from Chapter 1 that extraprostatic seed positions relative to the prostate are tightly specified at the BCCA, so implant radius is highly correlated to prostate radius. Determining the parameters for the TPS transform required the aggregation of seed displacement data between patients. As prostate size differs, seed positions in each patient were normalized to the distances of the peripheral seeds in their implants. The radius at the 95th percentile was arbitrarily chosen as this reference, assumed to be representative of the edge of the gland. Then, seed displacement vectors were assigned by origin to the closest of \( N = 1000 \) equal sub-volumes of the normalized space, obtained by dividing the space into a \( 10 \times 10 \times 10 \) grid. This was done for all patients in the cohort.

Directional statistics were evaluated for each of the populations of displacement vectors in each sub-volume. This involved fitting von Mises-Fisher distributions to the data, as was described in the previous Chapter (see Section 3.2.2). To briefly recapitulate, this distribution is parameterized by a unit direction vector \( \mu \), and a concentration parameter \( \kappa \), which play a similar role to the Gaussian mean and variance in describing the dispersion in direction of a population of vectors. Large values of \( \kappa \) in the context of the current study indicate that the seed displacements were tightly clustered around \( \mu \), whereas \( \kappa \to 0 \) implies that the displacement distributions were isotropic. Therefore, low values of \( \kappa \) indicate trends in seed dynamics that were common between patients, whereas high values indicate a lack of detectable systematic behaviour.

The TPS transformation in patient \( p \) of a seed with position \( \mathbf{r} = (x, y, z) \) at day-0 to a predicted position \( T_{p}^{TPS}(\mathbf{r}) \) at day-30 is given by Eqn. (4.4). In this equation, \( j \) indexes the aforementioned sub-volumes.

\[
T_{p}^{TPS}(\mathbf{r}) = \sum_{j=0}^{N} a_{j} \phi_{1}(\mathbf{r}) + \sum_{j=1}^{N} w_{j} U(\mathbf{r}, \mathbf{d}_{j}) : a \in \mathbf{a}, w \in \mathbf{w}
\]  

(4.4)

The coefficients \( a \) in the summation over the functions \( \phi_{1}(\mathbf{r}) = 1 \), \( \phi_{2}(\mathbf{r}) = r_{x} \), \( \phi_{3}(\mathbf{r}) = r_{y} \), and \( \phi_{4}(\mathbf{r}) = r_{z} \) represent the affine component of the transform, whereas the coefficients \( w \) in the summation over the basis function \( U(\mathbf{r}, \mathbf{d}) = \sqrt{\log(\|\mathbf{r} - \mathbf{d}\|) \log(\|\mathbf{r} - \mathbf{d}\|)} \) define the deformable components. The vector \( \mathbf{d}_{j} \) is the mean displacement of the seeds associated with the \( j^{th} \) sub-volume in the normalized space, weighted by the cube root of the ratio of the edema magnitude of patient \( p \) to the mean edema magnitude.

The formalism for the TPS transform used herein allows weights to be associated with each landmark, to control the strength of their effects on the non-affine elements of the deformation. This was historically
applied to redress variable noise in the spatial localization accuracy of each landmark. In this study the weighting is used to suppress non-rigid deformations in regions of the transform in which seed displacements were diffuse. The value of the weighting was $\sigma_j^2 = 1/n_j$, where $n_j$ is the number of seeds in the $j$th subvolume. Thus, sub-volumes in which displacement of a large number of seeds occurred in a consistent direction, induced a more pronounced local deformation of the TPS transformed coordinates in that region. Conversely, sub-volumes in which there was poor sampling of seeds, or where the directions of seed displacements were diffuse, contributed primarily to determining the affine components (coefficients $a$) of the transform. Note that because affine effects are global, an isotropic distribution of $d_j$ vectors among the sub-volumes would result in small values of the elements in $a$.

The coefficients $a$ and $w$ for a given set of landmarks can be determined by minimizing the TPS bending energy, resulting in a minimization problem which is independent in each dimension, with optimal coefficients given by the solution to Eqns. (4.5a,b). Associated matrix element definitions are given in Eqns. (4.5c-e). The $(3j \times 1)$ vector $v$ contains the components of the positions of centres of the subvolumes. The regularization parameter $\zeta$ controls the extent of non-rigid deformation, and was 0.001 for this study.

\[
(K + \zeta W^{-1})w + Pa = v \tag{4.5a}
\]
\[
P^Tw = 0 \tag{4.5b}
\]
where:
\[
K_{jj'} = U(d_j, d_{j'}) \tag{4.5c}
\]
\[
P_{jj'} = \phi(p_j) \tag{4.5d}
\]
\[
W_{jj'} = \begin{cases} \sigma_j^2 & j = j' \\ 0 & \text{otherwise} \end{cases} \tag{4.5e}
\]

It was recognized constructing a model partially informed by the data on which it would be validated would lead to unacceptable bias. Therefore, during evaluations, the coefficients of the TPS transform for each patient were derived using only the seed displacement data of the remaining patients.

4.2.6 Evaluation

Edema

Spearman’s $\rho$ was used to evaluate correlation between the different measures of edema magnitude. For the sake of interest, these were also compared to the ratio of CT volumes between day-0 and day-30, although this latter value was not used in the modeling component of this analysis.
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Distance-to-agreement

For each patient, the edema-corrected seed positions for each model were computed using Eqns. (4.2), (4.3), and (4.4) for the edema magnitudes described above. For the IE model, half-lives of 10, 15, and 30 days were used\(^{99,97,100}\). For the AL model resolution periods of \(T_E = 30, 45, \text{ and } 60 \text{ days}^{109}\) were used.

All seeds in the cohort were pooled for statistical analysis. The mean baseline DTA (\(D_{TA}^{baseline}\)) was calculated. The relative position error (RPE) for each model with respect to the baseline was then determined by Eqn. (4.6).

\[
\text{RPE}^{(model)} = \frac{D_{TA}^{(model)}}{D_{TA}^{baseline}} \times 100(\%) \tag{4.6}
\]

The distributions of DTA for each model were analyzed using two-way ANOVA to search for significant differences between the mean DTA after the application of different edema-correction models (IE, AL, TPS) and the baseline.

Loose seeds

Up to three loose seeds were available to the physician in order to rectify perceived lapses in dose coverage after the preplanned strands had been placed. A subset analysis was performed to investigate any differences in the RPE between loose and stranded seeds.

Dosimetric errors

The subset of edema model parameters that resulted in the lowest RPE was selected to investigate the dosimetric accuracy of edema correction. The absolute relative dosimetric error (RDE) between the dose predicted by the models (\(D^{(model)}\)) and the dose observed at day-30 (\(D(30)\)) was calculated for each voxel according to Eqn. (4.7) below. Cumulative histograms of the RDE were generated for each patient, which were then averaged over the cohort. The effect of using the model-predicted dose was compared to the baseline RDE derived from the day-0 dosimetry.

\[
\text{RDE}^{(model)} = \left| \frac{D^{(model)} - D(30)}{D(30)} \right| \times 100(\%) \tag{4.7}
\]

The TG-137 recommended dose-volume metrics for post-implant dosimetry were then determined from the dose distributions associated with each model. To do this, the prostate contours at day-0 were contracted as specified by each model. In the case of the TPS transform, the dose metrics were evaluated for the contours of both contraction models. Finally, to provide a perspective uninfluenced by contouring uncertainty, the total volumes encompassed by the 90%, 100%, 150% and 200% isodose surfaces at day-0, day-30, and for each of the model predicted distributions were also calculated and compared.
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**Strand length**
The median change in the length of strands between day-0 and day-30 was recorded. Results are reported for subsets of strands with the same number of seeds.

### 4.3 Results

#### 4.3.1 Measured Edema

The different estimates of edema for this cohort are summarized in Table 4.2. All uncertainties henceforth are one standard deviation. The mean pre-implant ultrasound derived prostate volume was 46.0±10.8 cm$^3$, and the mean day-0 post-implant CT-derived prostate volume was 54.3±16.4 cm$^3$. This corresponds to a mean relative increase in volume of 1.18±0.18 ($\Delta V_{CT(0)/US} = 0.18±0.18$). By day-30 post-implant, the mean prostate volume had fallen to 44.7±15.1 cm$^3$, or 0.97±0.20 of the pre-implant volume. The day-0 to day-30 CT volume ratio was 1.22±0.24 ($\Delta V_{CT(0)/CT(30)} = 0.22±0.24$). With respect to seed positions, the day-0 mean radial distance of 23.7±1.7 mm was 1.07±0.03 times larger than the cohort mean radial distance of 22.3±1.7 mm at day-30, resulting in a derived mean edema magnitude of $\Delta r = 0.21±0.10$. The differences between $\Delta V_{CT(0)/US}$, $\Delta V_{CT(0)/CT(30)}$, and $\Delta r$ were not significant.

Spearman’s $\rho$ was calculated to assess non-parametric correlation between the different methods of estimating edema magnitude to investigate consistency between the approaches. A correlation of $\rho = 0.10$ was found between $\Delta V_{CT(0)/US}$ and $\Delta r$, $\rho = 0.37$ between $\Delta V_{CT(0)/US}$ and $\Delta V_{CT(0)/CT(30)}$, and $\rho = 0.29$ between $\Delta r$ and $\Delta V_{CT(0)/CT(30)}$.

#### 4.3.2 Comparison of Predicted and Measured Day-30 Seed Positions

Figure 4.1 illustrates the effects of applying the TPS-transform, derived from seed displacements measured using only the average seed position to register day-0 to day-30 seed clouds, on a sagittal grid. This suggests that, on average, there is a rotation in seed positions around the centre of the implant during the first month. But is this seed migration, or a change in the pose of the whole gland? Consider Figure 4.2, which shows a single patient’s reconstructed day-0 implant overlaid on their day-30 implant. The internal consistency of strand alignment, and the misalignment of the average trajectory of the strands between time-points support the hypothesis that what is being witnessed is a rotation of the prostate as a whole. This may be due to differential edema in the various tissues surrounding the prostate, which cause the initial rotation at day-0. This observation motivated the application of a pose-correcting step during the registration of implants between time-points.
Chapter 4 – The post-implant dynamics of stranded seeds

### Edema characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Volume (cm$^3$)</td>
<td></td>
</tr>
<tr>
<td>Day-0 median (range)</td>
<td>52.3 (23.7 – 97.7)</td>
</tr>
<tr>
<td>Day-30 median (range)</td>
<td>40.6 (18.9 – 78.7)</td>
</tr>
<tr>
<td>Median volume ratios (range)</td>
<td>1.18 (0.74 – 1.53)</td>
</tr>
<tr>
<td>D0-CT/TRUS</td>
<td></td>
</tr>
<tr>
<td>D0-CT / D30-CT</td>
<td>1.29 (0.86 – 1.66)</td>
</tr>
<tr>
<td>($\bar{r}(0)/\bar{r}(30)$)$^3$</td>
<td>1.21 (1.08 – 1.39)</td>
</tr>
</tbody>
</table>

Table 4.2: Post-implant measurements of prostate volume and edema magnitude

The average pose correction was a 9.0±4.4° counter-clockwise rotation when viewed from the right sagittal perspective of the day-0 coordinate system. There was substantial patient specificity, as is evident from the standard deviation. No notable rotations were seen about the anterior-posterior (y) or superior-inferior (z) axes. This is consistent with the differential edema hypothesis, as there is much greater anatomical symmetry in these planes than in the sagittal.

The differences between the mean DTA after the application of the IE, AL, and TPS models were statistically significant, but only on the order of 0.1 mm. For the parameter combinations evaluated in this study, the RPE$^{IE}$ was a minimum of 87% for $\Delta=0.3$, and $\lambda_E = 10d$. Likewise, $\Delta=0.2$ and $T_E = 30d$ minimized the RPE$^{AL}$ at 89%. The DTA at these minima were $3.2 \pm 2.2$ mm (range 0.2 – 17.4 mm) and $3.3 \pm 2.2$ mm (range 0.2 – 18.5 mm), respectively. The mean DTA$^{TPS}$ and RPE$^{TPS}$ transform was $3.1 \pm 2.2$ mm (range 0.1 – 19.8 mm) and 85% respectively.

Pose-correction largely reconciled the differences in RPE between the TPS and contraction models. This is clear from the cumulative DTA histograms, shown with and without pose correction in Figure 4.3 for the minimizing model parameters given in the previous paragraph. There was some concern that the apparent differences in pose were due to isolated deflections of the strands in specific regions of the gland. To investigate whether this was the case, seeds were clustered by subdividing the gland into the standard quadrants (see Chapter 1). The mean baseline DTA was evaluated for each quadrant. As can be seen in Figure 4.4, the baseline DTA in all quadrants decreased after the pose correction, consistent with the hypothesis that the whole gland was rotated between scans.

After pose correction, the mean baseline and model DTA values were calculated. The mean DTA$^{baseline}$ was $3.7 \pm 2.3$ mm (range 0.2 – 15.0 mm). All mean and median model DTA results are presented relative to this baseline in Table 4.3. As can be seen from the tables, the results using edema magnitudes estimated from...
contour-based volumes ($\Delta^{CT(0)}_{US}$) were less accurate than when $\Delta'$ or fixed magnitudes of 0.2 – 0.4 were used.

Despite the improvement in RPE, there was substantial variability in the agreement between individual seeds and the predictions of the edema models: The DTA of approximately 30% of seeds increased from baseline after the application of any edema-correcting model.

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<th>$\Delta$</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
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<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>$\Delta'$</th>
<th>$\Delta^{CT(0)}_{US}$</th>
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<td>$\lambda_E = 10d$</td>
<td>0.3</td>
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<td>0.5</td>
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<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.4)</td>
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<td>(0.0)</td>
<td>(0.5)</td>
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<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
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<td>(0.2)</td>
<td></td>
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<tr>
<td>$\lambda_E = 20d$</td>
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<td>0.3</td>
<td>0.4</td>
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<td>(0.2)</td>
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<td>(0.4)</td>
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<td>(0.4)</td>
<td>(0.3)</td>
<td>(0.1)</td>
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</tbody>
</table>

Table 4.3: Mean (median) differences in mm between the model and baseline seed displacements using different parameter values in the isotropic and anisotropic edema models. The mean (median) baseline displacement was 3.7 (3.2) mm.

Seeds at the periphery of the implants were more likely to exhibit large displacements. The mean baseline DTA of seeds > 30 mm from the centre-of-implant was 4.6±2.6 mm compared to 3.0±1.6 mm for seeds < 15 mm from the centre (see Figure 4.5). However, the RPE$_{TPS}$ for the > 30 mm group was 78% versus 93% for the < 15 mm seed group. The corresponding RPE$_{IE}$ and RPE$_{AL}$ models were similar, and the differences statistically significant for all models (p < 0.05). This is consistent with contraction as the principal mechanism of systematic seed displacement, as Eqns. (4.2) and (4.3) both predict greater displacements for seeds further from the centre of the prostate.

The lengths of strands, measured as the sum of the distances between adjacent seeds which were stranded on day-0, were compared at day-0 and day-30. Although variance was large, strands of all lengths were significantly shorter on day-30 (p<0.001). The magnitude varied by the number of seeds. Those with three seeds (N=94) were shorter by a median of 1.4±2.3 mm, whereas those with four (N=184), five (N=262), and six (175) seeds were a median of 1.7±2.7, 2.3±3.5, and 2.9±4.2 mm shorter on day-30 respectively. This is less than what is predicted by the isotropic and anisotropic models for the superior-inferior axis, with which the strands are approximately parallel. Approximately 20% of strands appeared to shrink by more than 5 mm, and 2% had extended by more than 5 mm. It was observed that these latter cases
Chapter 4 – The post-implant dynamics of stranded seeds

typically involved a single gap between a pair of seeds from which seeds moved apart in well-spaced groups. This may imply that tensional forces acting on these strands were sufficient to induce point failures.

Figure 4.1: An illustration of the effect of the TPS transform before pose correction. A systematic rotation is evident between day-0 seed positions and day-30 seed positions. In the image above, the TPS transform is applied to a 10×10×10 cm grid.

Figure 4.2: Difference in pose between the day-0 and day-30 implant in one patient. The reconstructed paths of the strands at day-30 are red/solid while the blue/dotted lines represent the strands at day-0. The image on the left shows the implants prior to pose correction whereas the image on the right shows the implants afterward.
Figure 4.3: Cumulative histograms of the mean distance-to-agreement (DTA) between day-0 and day-30 seed positions with (TPS, Anisotropic, Isotropic) and without (Baseline) edema correction. The graph on the left shows the results with a pose correction whereas the graph on the right is without a pose correction. The TPS transform results in a substantially lower mean DTA than the contraction models if there is no pose correction as it implicitly includes a rotation of the implant between time points.

Figure 4.4: Means and 95% confidence intervals of the mean distance-to-agreement (DTA) of seeds stratified by prostate quadrant. The blue/circle markers represent the values after the pose correction. The red/square markers are the corresponding values without pose correction.
4.3.3 Loose Seed Subset Analysis

A total of 58 loose seeds were used in the cohort. A subset analysis was performed on these seeds to see how the DTA of loose seeds compared with those of the strands. The mean $\text{DTA}^{\text{baseline}}$ of these seeds was 4.0±2.1 mm, slightly but not significantly larger than the overall mean $\text{DTA}^{\text{baseline}}$ (ratio of loose-to-stranded median displacement: 1.07). When the IE, AL, and TPS transforms were applied to the day0 positions of the loose seeds, the loose-to-stranded mean post-correction DTA ratios were 1.0±0.5 (range: 0.5 – 2.7), 1.0±0.5 (range 0.5 – 2.6), and 1.0±0.5 (range 0.5 – 2.6) respectively. The displacement patterns of loose seeds implanted in this cohort did not exhibit significantly different behavior from their stranded counterparts.

4.3.4 Edema-corrected Day-0 versus Day-30 Dosimetry

The dosimetric analysis was confined to a subset of model parameters, as follows: For DVH metric calculations both $\Delta=0.2$ and $\Delta=0.3$ with $\lambda_E = 10d$ for the IE model, and $\Delta=0.2$ and $\Delta=0.3$ with $T_E=30d$ for the AL model were computed. However, for succinctness only the RDE results for $\Delta=0.3$ with $\lambda_E = 10d$ for the IE model and $\Delta=0.2$ with $T_E=30d$ for the AL model are presented. These were the values that approximately minimized the DTA for the respective models in the preceding analysis and are consistent with independent measurements of population average edema parameters\(^{97,100,192,194,205,206,207}\).

Histograms of the absolute RDE for each model were computed for the cohort. The histogram for the entire voxel grid is shown in Figure 4.6a. At day0, 49% of the voxels had an $\text{RDE}^{\text{baseline}}$ of <5%, while 72% and 89% had an $\text{RDE}^{\text{baseline}}$ of <10% and <20% respectively. Edema-correction using the TPS
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transform reduced the dosimetric error: 61% of the voxels exhibited an RDE\textsuperscript{TPS} of < 5%, 82% of voxels had an RDE\textsuperscript{TPS} of < 10%, and 94% of voxels had an RDE\textsuperscript{TPS} of < 20%. RDEs using the contraction models were ~2-3% larger than the TPS transform. In general, the edema-corrected dose was a more accurate representation of the day-30 dose distribution than the day-0 distribution, on a voxel-by-voxel basis.

As a surrogate for dose errors within the target volume, the RDE for voxels within a radius equal to the 95th percentile of the seed radii within each implant was calculated. The histogram for this subset is shown in Figure 4.6b. Reductions in RDE between baseline and the models were more pronounced in this region. The percentage of voxels with an RDE\textsuperscript{TPS} < 5% was 39%, whereas the percentage of voxels with RDE\textsuperscript{baseline} < 5% was 29%. Commensurate decreases in RDE were seen at the 10% and 20% levels as well, with the percentage of voxels with RDE\textsuperscript{TPS} < 10% equal to 60% (vs. RDE\textsuperscript{baseline} < 10% = 50%) and the percentage of voxels with RDE\textsuperscript{TPS} < 20% equal to 82% (vs. RDE\textsuperscript{baseline} < 20% = 75%).

The cohort mean dose metrics for day-0 and day-30 are shown in Table 4.4 for reference. Mean relative differences between the edema-corrected day-0 prostate dose metrics and the clinical day-30 dose metrics are presented in Table 4.5. Values greater than zero indicate that the model overestimated the parameter.

Paradoxically, the best predictors of V90, V100, D90 and D100 at day-30 were those at day-0, despite improvements in RDE when the models were used. Most of the dose metrics derived using edema models were significantly different from the actual day-30 values. With respect to D90 the differences were on the order of 20 Gy. The exception to this trend was the prostate V150 and V200, for which the contraction models at \(\Delta=0.2\) provided a better estimate of the day-30 dose metrics than the day-0 dose metrics.

The total volumes encompassed by the 90%, 100%, 150%, and 200% isodose surfaces were also compared. The mean differences between the day-0, TPS transformed, and contraction model volumes relative to day-30 are tabulated in Table 4.6. All edema-corrected dose volumes were significantly different from their day-30 values except for the TPS and AL (\(\Delta=0.3\)) models for V90, and the IE and AL (\(\Delta=0.2\)) models for V200. However, in general, the edema-corrected volumes tracked the day-30 values more closely than the day-0 values did. Simulating lower magnitudes of edema tended to more accurately describe the higher dose volumes, whereas higher edema magnitudes more accurately described the lower dose volumes.
### Post-implant Dosimetry

<table>
<thead>
<tr>
<th>Metric</th>
<th>Day – 0</th>
<th>Day – 30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D90 (Gy)</td>
<td>153.9±13.1</td>
<td>151.8±14.0</td>
</tr>
<tr>
<td>D100 (Gy)</td>
<td>81.9±15.4</td>
<td>77.3±15.8</td>
</tr>
<tr>
<td>V90 (%)</td>
<td>95.7±2.8</td>
<td>95.1±2.7</td>
</tr>
<tr>
<td>V100 (%)</td>
<td>92.1±3.8</td>
<td>91.8±3.6</td>
</tr>
<tr>
<td>V150 (%)</td>
<td>51.6±9.6</td>
<td>60.5±8.0</td>
</tr>
<tr>
<td>V200 (%)</td>
<td>17.7±6.7</td>
<td>28.6±6.1</td>
</tr>
<tr>
<td><strong>Urethra</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D0.1cc (Gy)</td>
<td>195.2±20.9</td>
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<td>D5 (Gy)</td>
<td>198.4±22.4</td>
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<td>D10 (Gy)</td>
<td>191.3±21.3</td>
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</tr>
<tr>
<td>D30 (Gy)</td>
<td>177.3±19.7</td>
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</tr>
<tr>
<td>V150 (cm³)</td>
<td>0.04±0.08</td>
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<tr>
<td><strong>Rectum</strong></td>
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<tr>
<td>D2cc (Gy)</td>
<td>96.0±18.5</td>
<td>111.8±20.6</td>
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<tr>
<td>D0.1cc (Gy)</td>
<td>155.8±37.7</td>
<td>182.3±32.5</td>
</tr>
<tr>
<td>V100 (cm³)</td>
<td>0.4±0.4</td>
<td>0.9±0.6</td>
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<tr>
<td><strong>Total</strong></td>
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<tr>
<td>V90</td>
<td>99.5±18.2</td>
<td>94.2±16.7</td>
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<tr>
<td>V100</td>
<td>88.4±16.0</td>
<td>84.3±15.1</td>
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<td>V150</td>
<td>39.9±6.4</td>
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<tr>
<td>V200</td>
<td>13.8±3.6</td>
<td>19.6±3.9</td>
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</table>

Table 4.4: Cohort mean post-implant dose metrics at day-0 and day-30
Chapter 4 – The post-implant dynamics of stranded seeds

<table>
<thead>
<tr>
<th>Prostate</th>
<th>V90 (%)</th>
<th>V100 (%)</th>
<th>V150 (%)</th>
<th>V200 (%)</th>
<th>D90 (Gy)</th>
<th>D100 (Gy)</th>
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<tr>
<td><strong>Day-0</strong></td>
<td>0.1±2.3*</td>
<td>-0.3±3.1*</td>
<td>-9.2±7.3</td>
<td>-11.2±7.0</td>
<td>-1.2±10.4*</td>
<td>0.1±16.0*</td>
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<tr>
<td><strong>TPS</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Δ_p^{{\text{iso}}} = 0.2</td>
<td>3.0±2.1</td>
<td>4.6±2.6</td>
<td>11.3±5.0</td>
<td>6.7±6.4</td>
<td>21.6±13.0</td>
<td>17.7±16.3</td>
</tr>
<tr>
<td>Δ_p^{{\text{iso}}} = 0.3</td>
<td>3.0±2.1*</td>
<td>4.4±2.6</td>
<td>10.6±5.1</td>
<td>6.0±6.4</td>
<td>20.4±13.0</td>
<td>17.5±17.1</td>
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<tr>
<td><strong>Isotropic (λ_E = 10d)</strong></td>
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<tr>
<td>Δ = 0.2</td>
<td>2.8±2.1</td>
<td>4.2±2.7</td>
<td>7.8±5.9</td>
<td>0.2±8.2*</td>
<td>18.9±13.3</td>
<td>13.7±17.1</td>
</tr>
<tr>
<td>Δ = 0.3</td>
<td>3.3±2.2</td>
<td>4.0±2.7</td>
<td>13.7±5.5</td>
<td>6.4±8.1</td>
<td>27.3±13.5</td>
<td>18.7±17.7</td>
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<td><strong>Anisotropic (T_E = 30d)</strong></td>
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<tr>
<td>Δ = 0.2</td>
<td>2.6±2.1</td>
<td>5.2±2.7</td>
<td>7.7±5.7</td>
<td>1.0±7.8*</td>
<td>18.2±13.1</td>
<td>14.2±16.8</td>
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<tr>
<td>Δ = 0.3</td>
<td>3.2±2.2</td>
<td>5.0±2.7</td>
<td>14.2±5.5</td>
<td>7.8±7.3</td>
<td>27.2±13.6</td>
<td>19.1±17.5</td>
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Table 4.5: Mean differences in prostate dose metrics relative to day-30. Positive values imply an increase in that parameter. Starred (*) values were not significantly different from zero at a significance level of 0.05.

Figure 4.6: Cumulative histograms of the effects of edema-correction on the mean relative dosimetric error (RDE). The baseline curve depicts the percentage of voxels that have less than the associated percentage RDE. As the edema-correction becomes more accurate, the curve shifts upwards and to the left. (a) The histogram for all voxels in an 80×80×80 mm volume centered on each implant. (b) The histogram for voxels within a sphere of radius equal to that of the 95th percentile of seed radii.
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<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>V90</th>
<th>V100</th>
<th>V150</th>
<th>V200</th>
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<tr>
<td>Day-0</td>
<td>5.3±3.1</td>
<td>4.1±2.6</td>
<td>-4.3±3.1</td>
<td>-5.8±2.4</td>
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<tr>
<td>TPS</td>
<td>0.6±2.1*</td>
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<td>3.4±2.3</td>
<td>2.3±1.7</td>
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<td>Isotropic (λE = 10d)</td>
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<td></td>
</tr>
<tr>
<td>Δ = 0.2</td>
<td>2.4±2.5</td>
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<td>4.5±2.6</td>
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<tr>
<td>Δ = 0.3</td>
<td>1.0±2.4*</td>
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<td>1.6±2.1</td>
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<tr>
<td>Anisotropic (T_E = 30d)</td>
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<td></td>
</tr>
<tr>
<td>Δ = 0.2</td>
<td>1.9±2.5</td>
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<td>2.4±2.2</td>
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<tr>
<td>Δ = 0.3</td>
<td>0.3±2.3*</td>
<td>0.9±2.1</td>
<td>4.6±2.8</td>
<td>2.4±2.1</td>
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</table>

Table 4.6: Mean differences in total isodose volumes (cm$^3$) relative to day-30. Positive values imply an increase in that parameter. Starred (*) values were not significantly different from zero at a significance level of 0.05.

4.3.5 Origin of Migrating Seeds

Twenty-five seeds that were present at day-0 could not be found inside the CT volume on Day-30. These were classified as distant migrations. This corresponds to 0.7% of all implanted seeds. An additional 9 seeds (0.2% of all implanted seeds) migrated locally, but were still near the implant volume. Most of these latter seeds were either on the posterior surface of the bladder, or in the seminal vesicles. The original positions of the migrating seeds at day-0 were determined, allowing possible mechanisms for migration to be deduced.

In five patients, the superior-most seeds of six strands that had been implanted into the seminal vesicles separated from their strands. In a seventh strand, two seeds had separated. In all but one patient, these locally migrating seeds were in the seminal vesicles. Of these, all but one shifted posterolaterally, with the remainder moving inferiorly along the posterior aspect of the prostate at the mid-sagittal plane. One seed located inside the seminal vesicles on day-0 was not present at day-30, likely expelled during ejaculation. The phenomenon of seed separation and local migration was specific to the strands implanted into the seminal vesicles.

Ten percent (32/338) of strands whose seeds’ mean position was inferior to the centre of the implant moved inferiorly as a group. This is contrary to what would be expected during a contraction. Of these, only three (0.4% of seeds) shifted by more than 5 mm inferiorly. In one dramatic example of the consequences of strand extraction, an anterolateral strand was pulled more than 3 cm posteroinferiorly. There was no obvious explanation for this event; at day-0, the most caudal seed in this strand was the most inferior of its immediate neighbors in that region of the prostate, but more than a centimetre superior of the inferior-most seeds of the neighbouring anteromedial strands, which did not exhibit any inferior displacement.
Twenty seeds, distributed among eight needles in seven implants, migrated distantly through the bladder wall. As all of these needles deposited seeds in close proximity to the bladder at day-0, it seems reasonable to hypothesize that they pierced the bladder wall while being maneuvered into position. Seeds were stranded in seven of the eight needles. Of these, one was located centrally, and the remainder positioned anteromedially. One needle of this set had been loaded with two loose seeds. At day-0, one of these seeds was already visibly inside the bladder, whereas the other was in the bladder wall. Both seeds were absent in the day-30 scan, suggesting that the second seed had migrated along the needle track and into the bladder. In one patient, two seeds from the cranial ends of a pair of anteromedial strands had presumably migrated into the bladder and subsequently lodged inside the urethra at day-30 (see Figure 4.7). It could not be determined whether these seeds were in transit or impeded by some persistent urethral obstruction. One concerning observation was the tendency for the remnants of strands which lost seeds to advance superiorly. This suctioning effect may account for the tendency towards multiple seed loss within strands that do transgress the bladder.

In four patients, five strands lost a single seed each, apparently directly into the urethra. In each case, the missing seed was always the most proximal to the catheter at day-0. In contrast to migration into the bladder, this was not a phenomenon of the superior-most seeds, nor was more than one seed ever witnessed to be lost by this route. There was also no evidence of the remaining seeds displacing in turn. Again, the anteromedial needles were at greatest risk - four of the strands were located in this region. The more central strand was the exception that proved the rule; the course of the urethra in that patient was unusually posterior where it intersected the strand.

In only one case did a seed from a laterally implanted strand migrate distantly. This strand was at the extreme left of the implant. The third of its four seeds was absent at day-30 and was presumed to have embolized, given its extraprostatic location. Chest films were not taken for these patients so it was not possible to determine if this seed became lodged in the lung. Imaging of the region in which the strand was implanted suggested no obvious anatomical explanation for this migration.
4.4 Discussion

At least three techniques have been proposed to assess the dosimetric uncertainties associated with edema. Chen et al.\textsuperscript{113} utilized the IE model to develop a method for describing the dose between points as a function of time, which they integrated over the life of the seeds. They evaluated the error associated with ignoring edema by calculating the difference between the planned dosimetry and dose distribution presuming the seeds and prostate displaced in synchrony with their model. This was performed for a range of edema magnitudes and half-lives. For edema magnitudes between 0.2 and 0.3 and half-lives between 10 and 15 days, they found that the dosimetric error relative to the plan was approximately 2 – 5%. For a magnitude of 0.5 and a half-life of 24 days, the error was 10%, and increased to 45% for a magnitude of 1.0 and a half-life of 100 days. This study found that the optimal post-implant interval for I-125 post-implant dosimetry was 42 days\textsuperscript{88}.
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For simplicity, the authors adopted a point-source dosimetric model that neglected anisotropy and scatter, a limitation that was later addressed by Leclerc et al.\textsuperscript{196}, who also applied the IE edema model to the prostate contours to interpolate dose-volume metrics. Leclerc et al. reported point differences of up to 10\% of the prescription dose in their analysis. More recently, Monajemi et al.\textsuperscript{109} considered the effects of anisotropic edema, motivated by clinical results from their institution\textsuperscript{97}. Like Chen et al., they computed the relative error on a per-voxel basis between the edema-corrected dose distribution and the planned dose. They found average errors of 2 – 4\% for edema magnitudes between 0.2 and 0.4. Errors increased with the edema magnitude and resolution time, up to \(\sim 7\%\) for a magnitude of 0.5 and resolution time of 56 days, and to \(\sim 20\%\) for a magnitude of 1.0 and a resolution time of 84 days.

The main purpose of this study was to try to assess the degree to which the dynamics of stranded seeds agree with prostate models of edema. The principal endpoint of this study was a distance-to-agreement measure because this metric is insensitive to contouring uncertainty. However, most studies pertinent to this investigation have not tracked individual seeds. Instead, post-implant seed dynamics have been inferred from sequential contour-based dosimetry. In general, these have shown trends consistent with contraction due to edema.

In 50 patients sequentially CT scanned at a mean interval of 46 days post-implant, Waterman et al.\textsuperscript{99} reported mean increases of 5\(\pm\)6\% in V100 and 15\(\pm\)17\% in D90. D'Souza et al.\textsuperscript{199} reported an increase in median V100 after the first month of 2.5\% in 40 patients. Reed et al.\textsuperscript{193} utilized MR in addition to CT in scans at a one-month interval. They found that although there were no significant changes in V100, D90 and V200 increased by 6 Gy (4\%) and 11\% respectively. MRI-CT fusion was also used by Taussky et al.\textsuperscript{100} in a series of 20 patients, who were scanned at three occasions post-implant: day-1, day-8 and day-30. Mean V100 increased slightly from 93.6\% to 96.3\%, while D90 increased by approximately 8 Gy. Steggerda et al.\textsuperscript{192}, who utilized stranded seeds, found a similar pattern of invariance in V100 and D90, with V150 increasing by a ratio of 1.25 at 3.5 months post-implant relative to day-1. Stranded seeds were also used by Pinkawa et al.\textsuperscript{200}, who reported small mean increases of 4\% in V100, but relatively larger increases of 11\% in V150, and 16 Gy (12\%) in D90. This trend was present again in the study by Saibishkumar et al.\textsuperscript{103}, who compared stranded to loose seed dosimetry using sequential MR-CT fusion. Between day-0 and day-30, V100 in their study was found to increase by a mean of 2 – 5\%, V150 by 15 – 19\%, and D90 by 9 – 23 Gy (ratio: 1.06 – 1.16).

Implants with excellent day-0 V100 may be unlikely to improve in that metric over the subsequent month\textsuperscript{100}, but rare is the study that has not shown an intensification of the high dose volumes during that period. The literature clearly supports the hypothesis that there is some degree of implant contraction, but there is little quantitative data on the strength of the correlation between seed and prostate dynamics.
Chapter 4 – The post-implant dynamics of stranded seeds

Our dosimetric parameters as they relate to biochemical control, as well as the BCCA’s experience with the efficacy of stranded versus loose seeds have been reported previously. While the focus of the present study was not to revisit the topic of stranded versus loose seeds, the extent to which the post-implant dynamics of stranded seeds are comparable to those of loose seeds is relevant, as some believe loose seeds track with the prostate, while stranded seeds do not, or do so grudgingly. There are concerns that the termini of strands become anchored in extraprostatic features such as the musculature of the pelvic floor, or the bladder wall. Inter-organ motion during edema may then cause these strands to be dragged from the prostate, as hypothesized by McLaughlin et al. Moerland et al. compared the dosimetry of stranded and loose seed implants by performing sequential analyses in the intraoperative setting and four weeks post-implant. They found that the use of strands augured poorer post-implant dosimetry, and attributed this to a similar mechanism as McLaughlin’s group.

In this study, the one striking example of inferior strand migration leaves little doubt that significant migrations of whole strands are a real risk. However, caudal displacements of > 5 mm were witnessed in only 0.4% of the strands, a relatively rare event. This risk is comparable to the increased risk of embolization when loose seeds are used. In two other cohorts, one of which was also from the BCCA, studies which set out to explicitly measure strand migration were unable to determine any systematic displacements, either with respect to pre-implanted fiducial markers or the penile bulb and bony landmarks. The only direct comparison between the geometric distribution of loose and stranded seeds at 4-6 weeks post-implant did not report a significant difference in the mean error of the seed positions relative to the preplan. For the typical implant therefore, the ability of strands to bend and compress is perhaps more relevant than the risk of anchoring and extraction. In our current study, strands were not an obvious impediment to contraction, as evidenced by the measurement of \( \Delta r = 0.21 \).

In practice, the theoretical results derived from edema modeling of loose implants have informed the recommended timing of all implant techniques. The equivalence in post-implant dynamics between loose and stranded-seed implants has been historically implicit in this context. While no significant differences were found between the mean DTA of the loose seed subset and the stranded seed subset in this study, the number of loose seeds available for analysis was small, precluding a broad generalization of these findings to loose seed implants.

The dispersions in seed displacements for seeds at the same relative distances from the centre of implant were quantified using directional statistics as part of the methodology to generate the TPS transform. The mean von Mises concentration parameter was 2.8, which signified considerable variance in the directions of displacement in each sub-volume. This result was not limited to extraprostatic seeds, which might be expected to have different dynamics from seeds within the gland. In fact, the reduction in RPE was significantly greater for seeds at the periphery of the implant.
In the present study, the agreement between the model-predicted seed positions and the day-30 data was generally poor. This was despite the use of patient-specific durations of resolution and estimates of edema magnitude to control for individual variability. It is perhaps unsurprising that there was little correlation between $\Delta^{CT(0)/US}$ or $\Delta^{CT(0)/CT(30)}$ with $\Delta'$. Counter to intuition, using patient-specific values of $\Delta'$ for edema-correction did not significantly reduce the mean DTA relative to the use of a population average (i.e. $\Delta=0.3$). This suggests that neither patient variability in estimated edema magnitude, nor scan timing was sufficient to explain why the RPE after correction remained as high as 85 – 89%. As RPE was high over a wide range of tested edema magnitudes, it is unlikely that the discrepancies between the model and the measurements were due to erroneous estimates of the magnitude alone. While the IE model was marginally more accurate than the AL model at predicting seed displacements, the differences in the mean DTA were on the order of 0.1 mm, and thus clinically inconsequential.

An important result of this study was that the TPS transform was also, in essence, a contraction, and broadly mimicked the behaviour of the contraction models. The degree of similarity is visualized in Figure 4.8, which shows the effects of each model on a uniform grid from different perspectives. Thus, to the extent that a pattern for systematic seed displacement was found to exist, it broadly agrees with the independently published prostate models. However, seed displacement is highly variable, and thus the robustness of any edema-corrected dosimetry predicated on these models is questionable.

In general, the dosimetry of this cohort is typical for the BCCA. With respect to clinical dosimetric endpoints, neither D90 nor V100 changed significantly between day-0 and day-30 (p=0.57 and p=0.68 respectively). In contrast, increases in V150 and V200 were highly significant (p < 0.001). The discrepancy between increases in these high-dose volume measures with a stable D90 is consistent with an earlier observation that whole prostate D90 at our institution is highly correlated with the coverage of the anterior superior quadrant (ASQ) of the gland\cite{93,130}. Seed density is typically sparse in the ASQ because of the lack of implantable tissue in that region and concern about urinary toxicity. Thus, it appears that the resolution of edema does not result in a pronounced intensification of dose in this region, and whereas V150 can be driven up by increases in the remainder of the gland, D90 is typically determined in the ASQ.

The tenuous agreement between the displacements of individual seeds and the edema models was recapitulated in the dosimetric analysis. Even using the parameters for each model that minimized DTA, more than 18% of the voxels in the central region of the edema-corrected dose distributions had an RDE of greater than 20%. Seed loss may partially explain some of this variation, but even the subset of patients who suffered no distant migration (62%) had RDEs similar to those that did (data not shown).
A critical aspect of the design of this study was the exclusion of contouring and anatomical landmarks from the registration. Seed clouds were directly registered together using the centre of implant and the average orientation of the strands at each time-point. The inclusion of strand orientation in the registration criteria (‘pose-correction’) resulted in a reduction in the mean DTA of 26% compared to when only the centre-of-implant was used. The decrease in mean DTA after pose correction was witnessed in all prostate quadrants, suggesting that the effect was not the result of a regional compromise that might be expected if
strands were deflecting in only the base or apex. Sloboda et al. found it necessary to rotate the long axes of the prostate to register the structure on sequential scans in their study\(^\text{97}\). However, the average rotation that was necessary to realign strands in the present work (9.0°) was significantly larger than in their study (1.3°). In addition to translations of the gland\(^\text{103,105,192,200}\), our results suggest that edema in the genitourinary diaphragm and other structures adjacent to the gland may introduce a more pronounced rotation at day-0 than previously thought.

The principal advantages of the registration methodology used herein are that it is objective and easily reproducible. The suitability of the centre-of-implant as a reference point for the prostate is vetted by some of the aforementioned studies which found shifts on the order of 1 mm of this point with respect to the prostate between day-0 and day-30\(^\text{107}\). The occasional migration of a strand is unlikely to substantially affect the average position of the implant. Nonetheless, it is worth highlighting limitations and possible pitfalls. No anatomical landmarks informed the registration. This risks conflating rotation of the gland with variations in patient setup, and shifts in entire implant relative to the prostate to translations of the gland itself. It has also been assumed that the prostate and implant contract centrally, rather than towards some other position. A misconception in this regard would result in systematic errors in measured displacements under the contraction models. However, scenarios such as this were what the TPS transform was designed to (and did not) find.

There will be some that perceive registration based on anatomical landmarks to mitigate these types of problems, but there are attendant limitations in such methods as well. Accurate prostate definition is a challenge, to which numerous studies of inter-observer contouring variability attest\(^\text{101,209,210,211}\). The use of MRI has been shown to reduce these uncertainties relative to CT\(^\text{212,213,214}\). Even so, it is telling that standard deviations of 2 – 4 mm persist in estimates of gland dimensions, even among experts in the same centre, with harmonized training, in a study setting\(^\text{107}\). For longitudinal migration studies such as the present one, contouring uncertainties would be compounded first by variability in the CT-MRI fusion process\(^\text{215,216}\), and then by the registration between day-0 and day-30. It is by no means certain that this latter process, involving glands of different volume and pose would require fewer a priori assumptions than have been necessary herein. The potential for the propagation of error is considerable, and its impact difficult to discern without tedious multi-observer controls.

### 4.5 Conclusions

Stranded seed displacement is highly variable, both in magnitude and direction. Current models for prostate edema weakly predicted the dynamics of stranded seeds after one month, with a mean RPE of 87 – 89%. A TPS-based transformation was fit to measured seed displacements to determine if systematic displacements existed that were not captured by the prostate models. This transform resulted in a mean
RPE of 85%, broadly reproducing the behaviour of the prostate models in geometric effect as well as RPE reduction. With respect to dosimetry, although edema-correction of the day-0 dose distribution resulted in closer agreement with the day-30 distribution on a voxel-by-voxel basis, and by total isodose volume, this did not translate into more accurate prostate dose metrics. This paradox is likely due to the dependence of the latter on contouring, which is highly variable on CT. While this study was principally conducted on strands, a limited analysis of loose seeds did not suggest that they exhibited any greater correlation with the models. Seed loss in stranded implants is primarily associated with the anterior base, when strands advance into the bladder, or when strands intersect the urethra.
5 Dosimetric Outcomes of Simulated Mixed-activity Implants

5.1 Introduction

The current practice for PIPB is to use seeds of a single activity, or corresponding air-kerma strength (U). I-125 implants have been performed using seed strengths ranging from 0.42U – 0.84U. Choice of seed strength is often correlated with the technique, specifically with the tendency to implant the extraprostatic tissue. Institutions which implant seeds in the extraprostatic tissue, such as the BCCA, tend to use lower activities than those which aim to confine the seeds to the prostate capsule. A number of previous studies have investigated the effects of utilizing different seed activities in permanent prostate implants, and elucidated a number of trade-offs between high and low strength implants. In general, increasing source activity reduces the number of needles and consequent trauma, at the cost of diminished conformity and dose homogeneity. The concern among many physicians who prefer low activity implants is the potential for fistula following the misplacement or migration of a high activity seed, as such complications can result from isolated hot-spots. As a result, there is no consensus on the optimal seed activity.

The basic premise of this chapter is that there may not be a single ideal source activity for prostate implants. Rather, the solution may be to vary the seed activity depending on the location of the seed within the gland. In HDR brachytherapy, the source dwell times at each position can be varied to spatially modulate and optimize the dose distribution. The same rationale applies to PIPB. ‘Mixed-activity’ treatment planning is more flexible: Dose can be shaped by scaling activity as well as modifying seed positions to improve conformity and avoid dosing normal tissues.

The risk of seed misplacement depends on the anatomical location at which a seed is planned. Poor ultrasound contrast at the prostate-bladder interface can result in seeds being planned in the bladder wall, which consists of tissue that is challenging to implant. Seed trains in this region have been noted to diverge laterally as they are inserted due to frictional forces and gland rotation. Moreover, the pubic arch, which is difficult to identify on ultrasound, routinely occludes planned anterolateral needle paths, requiring difficult needle steering maneuvers which further exacerbate the uncertainty in seed placement. These effects contribute to well-documented post-implant coverage deficits in this region.

As was shown in the previous chapter, strand fixity in the post-implant interval is also a function of location. Seeds implanted near the bladder, or in proximity to the urethra, are at greater risk of distant migration. The superior-most seeds of strands implanted into the seminal vesicles may detach and float away from the target volume. The consequences of seed placement uncertainty with respect to target coverage and collateral dose to organs-at-risk are similarly dependent on the neighborhood of the planned
source position. In one study, the maximum rectal dose was strongly associated with the position of seeds in the posterior apex of the gland. Mixed activity implants may improve the robustness of post-implant dosimetry to edema by giving treatment planners the capacity to deliver a curative dose without having to plan seeds in risky locations.

The aim of this chapter is to describe a study in which mixed activity implants were simulated in a cohort of patients. Four plans were created for each patient: a standard low activity plan, a high activity plan, and two mixed activity plans. The standard plan was implanted according to current BCCA clinical protocol. Post-implant imaging was acquired at both day-0 and day-30. Post-implant analysis and plan reconstruction was performed at both time-points. Using the plan reconstruction, a correspondence was established between the treatment plans and the post-implant seed distributions. The high and mixed-activity plans were then mapped into the post-implant CT space, and the resulting dosimetry compared to the low-activity plans.

5.2 Methods

5.2.1 Cohort

The cohort for this study is the same as that described in Chapter 4.

5.2.2 Planning Arms

Four planning arms were created for each patient in the cohort. All planning arms were required to conform to the BCCA planning guidelines that were introduced in Section 1.2.4. Where minor deviations from the guidelines were necessary, such as clipping of the 100% isodose line with the PTV, these were consistent with clinical practice. Arm-1, also referred to herein as the ‘control’, was the standard clinical plan that had been used to implant the patient (seed strength = 0.427U). In order to simulate the effects of seed misplacement and migration, seed placement in the experimental arms (Arms 2, 3 and 4) was restricted to any subset of the template positions utilized by the clinical arm.

Arm-2 consisted of seeds with uniform activity of 0.6U. This was the highest activity at which it was deemed feasible to meet the dosimetric goals outlined in Chapter 1 during planning. Arm-3 was a mixed-activity arm, containing seeds of either 0.4U, 0.6U or 0.9U. Seeds of 0.9U were not permitted to be planned inferior to the apex, in the central posterior, or in positions adjacent to the expected course of the urethra. These restrictions are illustrated in Figure 5.1. Arm-4 had the same spectrum of activities as Arm-3, but the number of needles used in the plan was reduced as much as possible. The aim of Arm-4 was to determine whether aggressively reducing needle counts using the flexibility of mixed-activity methodology would result in any detriment to dosimetry relative to Arm-3, which preserved a more traditional needle distribution.
Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

5.2.3 Simulation of Experimental Plans

The post-implant dosimetry of the experimental arms was calculated by mapping the activities of seeds in these plans into the post-implant CT data using the correspondence elucidated by plan reconstruction. This assumes seed placements in the experimental arms would have been identical to that in the clinical arm for seeds which shared the same planned position, a reasonable assumption since displacement and migration are a consequence of biomechanical factors, not seed activity. Any seeds which were not used by the experimental arms were deleted from the post-implant analysis of those arms. However, where discretionary, unplanned seeds had been implanted during the procedure, these were retained in all arms at their utilized strength (0.42U).

5.2.4 Contouring

Structures assessed were the prostate and rectum at day-0 and day-30, and the urethra at day-0, as the latter could only be reliably delineated in presence of the catheter at that time. To address the issue of inter-observer contouring variability, each structure was contoured by three observers, who were blinded to the contours of their colleagues, as well as their own day-0 results during day-30 contouring. Due to the presence of the catheter, it was not possible to randomize the chronology of the images to control for expectation bias with respect to edema.

5.2.5 Evaluation

Summary statistics of the TG-137 recommended primary and secondary DVH parameters for the prostate and rectum at day-0 and day-30, and the urethra at day-0, were computed. The conformity index (CI) was also determined to assess extra-prostatic dose. To examine the ability of mixed-activity implants to enhance dose in the anterior base of the prostate, dose metrics by prostate quadrant were also calculated.
Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

The paired differences in each endpoint between each arm were assessed using a one-way ANOVA. For significance testing, the Tukey-Kramer method for multiple comparisons between arms was used with a significance level of 0.05. The average differences between the total activity, number of seeds, and number of needles were also calculated.

Rather than attempting to construct a single representative post-implant structure from the individual contours produced by the observers, all analyses was repeated for the contours of each observer. In the associated tables, the results of individual observers are shown by row for each arm. The fourth row in each arm is the pooled-observer (PO) result, in the form of the mean and standard deviation of each parameter for all observers. Given the volume of data considered, only results in which at least one observer reported a change significantly different from zero will be discussed further. Differences in dose metrics between the experimental arms and the clinical control (Arm-1) for which there was greater consensus among the observers were considered to be more reliable evidence of effect.

5.3 Results

5.3.1 Planning

As a consequence of adhering to the BCCA guidelines, V100, V150 and V200 in each arm were within the range specified in Chapter 1. The cohort mean D90, V100, V150, and V200 in the control-arm was 179±4.0 Gy, 99.4±0.6%, 63.5±2.5%, and 19.9±2.8% respectively. Uncertainty in these values reflects the standard deviation between cases. Mean paired differences in planned dose metrics with respect to the control-arm are shown in Table 5.1.

Most parameters were significantly different from their counterparts in the control-arm. However, the differences in D90 and V100 were generally minor, with V100 varying by < 0.3% on average. Only Arm-2 had a D90 significantly different from the control, amounting to 2% in relative terms. Changes in the high dose regions were more prominent, especially the decreases in V200 in the mixed activity arms.
Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

<table>
<thead>
<tr>
<th>Arm</th>
<th>V100 (%)</th>
<th>D90 (Gy)</th>
<th>V150 (%)</th>
<th>V200 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.0±0.6</td>
<td>-2.7±4.6*</td>
<td>-3.7±3.1*</td>
<td>-0.5±2.8</td>
</tr>
<tr>
<td>3</td>
<td>0.3±0.3*</td>
<td>1.2±3.8</td>
<td>-1.5±3.2*</td>
<td>-2.7±2.7*</td>
</tr>
<tr>
<td>4</td>
<td>0.2±0.4*</td>
<td>1.1±3.4</td>
<td>-2.4±3.3*</td>
<td>-2.6±3.3*</td>
</tr>
</tbody>
</table>

Table 5.1: Mean paired difference in selected planned PTV dose metrics between the experimental arms and the control. Negative values imply the dose metric was lower in the experimental arm than the control. Asterisks indicate significance.

5.3.2 Whole Prostate Dosimetry

The cohort-averaged primary and secondary dose metrics for the prostate are shown in Table 5.2 and Table 5.3, respectively. In Table 5.4, significant differences in the TG-137 endpoints for the prostate, urethra and rectum are colour-coded to indicate the number of observers that found a difference to be significant. The high activity arm (Arm-2) had slightly cooler dosimetry overall. For the contours of two of the observers, V100, D90 and V150 all decreased slightly at day-0, although this was not significant by day-30. In comparison, V100 and D90 in the mixed activity arms were slightly higher. While this was only noted in the data by a single observer at day-0, by day-30 the impact became more pronounced, particularly in Arm-4, where V100 and D90 improved at day-30 according to all observers.

The improved coverage in the mixed activity arms was not accompanied by an increase in V150 or V200. Instead, V150 in both these arms was on average lower than the control-arm at day-0. Results from one observer also showed a decrease in V200 at day-0 in Arm-3. Overall, from a whole prostate perspective, the impact of the experimental plans was minimal.

The conformity index by arm is shown in Table 5.5. On day-0, the control-arm had the best conformity on all observer contours, while Arm-2 had the poorest. This difference was significant. The mixed-activity arms had indices that fell between these extremes. There were no significant differences between Arms 3 and 4, but they both differed significantly from Arm-2 and the control. In general, conformity was poorer in all Arms at day-30 than day-0. With the exception of one observer at this time point, for whom the difference between CI in Arm-2 and 3 approached but did not reach significance, the same relative differences in conformity between the arms were observed.
## Table 5.2: Cohort means ±1 SD for the primary prostate endpoints.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Obs.</th>
<th>Day-0 V100 (%)</th>
<th>Day-30 V100 (%)</th>
<th>Day-0 D90 (Gy)</th>
<th>Day-30 D90 (Gy)</th>
<th>Day-0 V150 (%)</th>
<th>Day-30 V150 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ctrl</td>
<td>92 ±5 89 ±7</td>
<td>151 ±14 141 ±22</td>
<td>48 ±12 54 ±9</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>91 ±4 93 ±3</td>
<td>148 ±12 156 ±12</td>
<td>50 ±9 61 ±9</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>89 ±4 86 ±6</td>
<td>142 ±13 132 ±20</td>
<td>48 ±10 53 ±10</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>91 ±4 89 ±6</td>
<td>147 ±13 143 ±21</td>
<td>49 ±10 56 ±10</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Table 5.3: Cohort means ±1 SD for the secondary prostate endpoints.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Obs.</th>
<th>Day-0 V200 (%)</th>
<th>Day-30 V200 (%)</th>
<th>Day-0 V90 (%)</th>
<th>Day-30 V90 (%)</th>
<th>Day-0 D100 (Gy)</th>
<th>Day-30 D100 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ctrl</td>
<td>16 ±8 25 ±8</td>
<td>96 ±3 93 ±6</td>
<td>95 ±19 84 ±24</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>18 ±7 30 ±8</td>
<td>95 ±3 97 ±4</td>
<td>82 ±11 93 ±16</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>17 ±7 26 ±8</td>
<td>94 ±4 91 ±6</td>
<td>76 ±13 68 ±21</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>17 ±7 27 ±8</td>
<td>95 ±3 94 ±5</td>
<td>84 ±17 82 ±23</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15 ±6 25 ±7</td>
<td>95 ±4 93 ±6</td>
<td>93 ±17 86 ±25</td>
<td>5</td>
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<td>19 ±6 30 ±7</td>
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<td>82 ±11 94 ±18</td>
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</tr>
<tr>
<td>P</td>
<td></td>
<td>18 ±5 26 ±7</td>
<td>93 ±4 91 ±6</td>
<td>77 ±13 70 ±21</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>14 ±6 24 ±8</td>
<td>97 ±4 94 ±6</td>
<td>100 ±20 88 ±25</td>
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<tr>
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<td></td>
<td>17 ±6 29 ±9</td>
<td>96 ±3 97 ±3</td>
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<tr>
<td>4</td>
<td></td>
<td>16 ±6 26 ±9</td>
<td>96 ±4 94 ±6</td>
<td>90 ±17 86 ±23</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2: Cohort means ±1 SD for the primary prostate endpoints.

Table 5.3: Cohort means ±1 SD for the secondary prostate endpoints.
<table>
<thead>
<tr>
<th></th>
<th>Arm 2 – Ctrl</th>
<th>Arm 3 – Ctrl</th>
<th>Arm 4 – Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day-0</td>
<td>Day-30</td>
<td>Day-0</td>
</tr>
<tr>
<td>V100</td>
<td>-4.3 [-2.3 -0.4]</td>
<td>0.4 [-1.3 2.1]</td>
<td>0.4 [-1.3 2.2]</td>
</tr>
<tr>
<td>D90</td>
<td>-7.7 [-3.9 -0.0]</td>
<td>1.4 [-4.7 8.0]</td>
<td>3.2 [-5.0 9.2]</td>
</tr>
<tr>
<td>V150</td>
<td>-5.6 [-3.0 -1.7]</td>
<td>0.1 [0.8 -1.4]</td>
<td>0.1 [0.8 -1.4]</td>
</tr>
<tr>
<td>V90</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>V200</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>D100</td>
<td>3.0 [0.5 2.7]</td>
<td>0.3 [1.0 6.9]</td>
<td>0.4 [1.0 6.9]</td>
</tr>
<tr>
<td>D5</td>
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<td>2.7 [6.7 10.7]</td>
<td>2.7 [6.7 10.7]</td>
</tr>
<tr>
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<td>1.9 [5.3 8.8]</td>
<td>2.3 [5.7 9.1]</td>
</tr>
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</tr>
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<td>2.6 [6.0 9.5]</td>
<td>3.3 [7.3 11.3]</td>
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<td>NS</td>
<td>NS</td>
</tr>
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<td>1.6 [5.4 9.3]</td>
</tr>
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<td>1.8 [19.4 37.1]</td>
<td>3.4 [9.9 16.5]</td>
<td>NS</td>
</tr>
<tr>
<td>V100</td>
<td>0.06 [0.18 0.32]</td>
<td>0.03 [0.21 0.38]</td>
<td>0.03 [0.21 0.38]</td>
</tr>
</tbody>
</table>

**Legend**

μ: mean, μ±95%CI: mean ± 95% confidence interval, NS: no significance

**No. of observers with a significant result**

- **Obs #1**: 0
- **Obs #2**: 0
- **Obs #3**: 0

Table 5.4: Means of the patient-paired differences in structure endpoints. The null hypothesis was a zero mean difference. Differences for which no observers showed a significant result are not listed.
## Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

### Table 5.5: Conformity index ±1 SD.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Obs.</th>
<th>CI</th>
<th>Day-0</th>
<th>Day-30</th>
</tr>
</thead>
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<td>1</td>
<td>2.9 ±0.7</td>
<td>2.5 ±0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.9 ±0.3</td>
<td>2.2 ±0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.7 ±0.3</td>
<td>1.9 ±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2.2 ±0.7</td>
<td>2.2 ±0.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>2.7 ±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.0 ±0.3</td>
<td>2.3 ±0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.9 ±0.3</td>
<td>2.1 ±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2.3 ±0.7</td>
<td>2.3 ±0.5</td>
<td></td>
</tr>
<tr>
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<td>1</td>
<td>3.0 ±0.7</td>
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</tr>
<tr>
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<td>1.9 ±0.3</td>
<td>2.3 ±0.4</td>
<td></td>
</tr>
<tr>
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<td>2.0 ±0.5</td>
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</tr>
<tr>
<td></td>
<td>P</td>
<td>2.2 ±0.7</td>
<td>2.3 ±0.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
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<td>2.6 ±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.9 ±0.3</td>
<td>2.2 ±0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.8 ±0.3</td>
<td>2.0 ±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2.2 ±0.7</td>
<td>2.3 ±0.5</td>
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</tr>
</tbody>
</table>

Table 5.6: Cohort means ±1 SD for the urethral endpoints (Day-0).
Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

<table>
<thead>
<tr>
<th>Arm</th>
<th>Obs.</th>
<th>RD2cc (Gy)</th>
<th>RV100 (cm³)</th>
<th>RD0.1cc (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day-0</td>
<td>Day-30</td>
<td>Day-0</td>
</tr>
<tr>
<td>1</td>
<td>Ctrl</td>
<td>1</td>
<td>114 ±26</td>
<td>126 ±23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>93 ±19</td>
<td>112 ±21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>89 ±20</td>
<td>104 ±19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>99 ±24</td>
<td>114 ±23</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1</td>
<td>119 ±31</td>
<td>132 ±26</td>
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<td></td>
<td></td>
<td>2</td>
<td>98 ±21</td>
<td>117 ±23</td>
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<td>3</td>
<td>93 ±22</td>
<td>109 ±20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>103 ±27</td>
<td>119 ±25</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
<td>115 ±27</td>
<td>127 ±25</td>
</tr>
<tr>
<td></td>
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<td>114 ±22</td>
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<td>105 ±19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>100 ±24</td>
<td>115 ±23</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1</td>
<td>114 ±33</td>
<td>126 ±27</td>
</tr>
<tr>
<td></td>
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<td>94 ±22</td>
<td>113 ±23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>89 ±23</td>
<td>104 ±20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>99 ±28</td>
<td>114 ±25</td>
</tr>
</tbody>
</table>

Table 5.7: Cohort means ±1 SD for the rectal endpoints.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Total</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 1.0cc</td>
<td>→1</td>
</tr>
<tr>
<td>1 (Ctrl)</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>0</td>
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<td>3</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5.8: Impact on RV100 between arms for a 1.0 cm³ threshold. The values in grey are the number of patients who did not receive an RV100 > 1.0 cm³, but who would have had they been treated with the arm indicated by the column, rather than the arm indicated by the row. The total column lists the number of patients whose PO RV100 > 1.0 cm³.
5.3.3 Urethral and Rectal Dosimetry

Urethral dosimetry was only available on day-0, as there was no catheter in place at day-30. Overall, urethral dose in all arms was within the expected range, and is shown in Table 5.6. In no arm did a mean UD10 > 150% occur for any observer, nor a UD30 > 130%. These thresholds are the TG-137 recommended planning tolerances for the urethra. However, urethral dose in the mixed activity arms increased overall by a small amount: approximately 3% in UD10 and 2% in UD30.

The rectal dose metrics, shown in Table 5.7, were consistently higher in Arm-2 than in the rest of the cohort. From the perspective of the RV100, increases of between 0.16 cm$^3$ and 0.21 cm$^3$ at day-30 were seen for all observers. This has potential clinical impact, as it increased the PO mean to lie over the 1.0 cm$^3$ threshold found by Herstein et al.\textsuperscript{227} to increase the risk of radiation proctitis. Minor increases in both RD2cc and RD0.1cc were also noted in this arm. In comparison, rectal doses in the mixed activity arms were statistically indistinguishable from the controls.

However, as deleterious rectal dosimetry tends not to be normally distributed, the absolute number of patients in each arm with suboptimal rectal dosimetry\textsuperscript{88} (RV100>1.0cm$^3$) is shown in Table 5.8. This table also indicates the number of patients in each arm who would have exceeded that threshold had they been treated in a different arm.

5.3.4 Quadrant Dosimetry

The primary and secondary dose metrics were calculated for each quadrant of the prostate. Cohort means and standard deviations for the anterior and posterior quadrants are shown in Table 5.9 and Table 5.10, respectively. Parameters in which there were significant differences between the experimental and the control-arms are highlighted in Table 5.11 and Table 5.12. Overall, coverage of the PSQ, PIQ, and AIQ was excellent in the control-arm. PO-V100 and PO-D90 in these regions generally exceeded 95% and 160 Gy respectively. In contrast, coverage in the ASQ was poor, a finding that is consistent with previous studies at the BCCA\textsuperscript{93,130}. At day-0, the mean PO ASQ-V100 was 72%, and the mean PO ASQ-D90 was 119 Gy (82% mPD).

The use of higher activity seeds in Arm-2 did not result in any significant changes to dose metrics in the ASQ at either day-0 or day-30. In contrast, both mixed activity arms had significantly improved coverage in this region with respect to ASQ-V100 and ASQ-D90. At day-0, the contours of two observers showed a mean ASQ-V100 increase in Arm-3 of ~4%. In Arm-4, the contours of all three observers showed an increase of ~5% in this metric. These improvements were still evident at day-30, with the same proportions of observer contours showing increases of ~4% in Arm-3, and ~5% increases in Arm-4. D90 increased at day-0 and day-30 in both mixed activity arms for all observers. At day-0, ASQ-D90 was ~7 Gy higher in
Arm-3, and ~9 Gy higher in Arm-4. Comparable improvements were seen at day-30. Concurrent increases in the high-dose metrics (ASQ-V150, ASQ-V200) of ~2% were also seen in these Arms.

There were only minor changes in the AIQ dosimetry. All contour sets showed a ~6 Gy increase in the AIQ-D100 of Arm-2 relative to control at day 0. The contours of a single observer showed similar increases in this metric in the mixed-activity arms, but these did not endure to day-30. Likewise, differences in the PSQ were generally confined to day-0. Paradoxically, Arm-2 had a diminished PSQ-V100 and PSQ-D90, but a higher PSQ-V200 at day-0. This increase was still evident at day-30. The mixed-activity arms experienced decreases in PSQ-D90 of ~8 Gy in this region, but only at day-0.

The PIQ was the hottest quadrant, with a PO PIQ-V150 of 89% and a PO PIQ-V200 of 52%. Arm-2 generally displayed reductions in most dose metrics in this region at day-0, particularly PIQ-D90, which decreased by ~4 Gy relative to baseline at this time point. By day-30, this gap had grown to ~6 Gy for all observers. A decrease in PIQ-V150 at day-0 was seen for one observer, but this was not robust. No changes were noted in PIQ-V200. In comparison, the mixed-activity arms both experienced decreases in PIQ-D90. In Arm-3, this parameter decreased by ~5 Gy at day-30. In Arm-4, one observer showed a decrease of 4 Gy at day-0, and a consensus showed decreases of ~7 Gy on day-30. The mixed-activity arms also had significant decreases in the high dose metrics at both day-0 and day-30. PIQ-V150 and PIQ-V200 reductions were ~4%. PIQ-D100 also decreased by up to 9 Gy in these arms.
## Table 5.9: Primary dose metrics for the anterior prostate quadrants. Values are cohort means ±1 SD.
### Table 5.10: Primary dose metrics for the posterior prostate quadrants. Values are cohort means ±1 SD.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Obs.</th>
<th>V100 (%)</th>
<th>D90 (Gy)</th>
<th>V150 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day-0</td>
<td>Day-30</td>
<td>Day-0</td>
</tr>
<tr>
<td>1 (Ctrl)</td>
<td>1</td>
<td>98 ±3</td>
<td>94 ±10</td>
<td>179 ±23</td>
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<td>97 ±4</td>
<td>175 ±22</td>
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<td>94 ±8</td>
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<td>100 ±1</td>
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<td>100 ±0</td>
<td>188 ±24</td>
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</table>
### Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

<table>
<thead>
<tr>
<th>Mean paired difference</th>
<th>Arm 2 – Ctrl</th>
<th>Arm 3 – Ctrl</th>
<th>Arm 4 – Ctrl</th>
</tr>
</thead>
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<td>Day-0</td>
<td>Day-30</td>
<td>Day-0</td>
</tr>
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<td>V100</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
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<td>NS</td>
<td>3.5 6.2 4.8</td>
<td>4.7 5.1 10.6</td>
</tr>
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<td>NS</td>
<td>4.8 7.4 10.1</td>
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</tr>
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<td>NS</td>
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<tr>
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<td>NS</td>
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<td>0.3 1.2 6.0</td>
</tr>
<tr>
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<td>NS</td>
<td>0.3 3.0 5.8</td>
<td>1.6 3.4 5.2</td>
</tr>
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<td>NS</td>
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<td>0.3 1.2 6.0</td>
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<td>NS</td>
<td>0.3 1.2 6.0</td>
<td>0.3 1.2 6.0</td>
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<tr>
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<td>NS</td>
<td>0.3 1.2 6.0</td>
<td>0.3 1.2 6.0</td>
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<td>V90</td>
<td>NS</td>
<td>0.3 1.2 6.0</td>
<td>0.3 1.2 6.0</td>
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<td>NS</td>
<td>0.3 1.2 6.0</td>
<td>0.3 1.2 6.0</td>
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<td><strong>μ+95%CI</strong></td>
<td><strong>NS = no significance</strong></td>
</tr>
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<td><strong>μ+95%CI</strong></td>
<td><strong>NS</strong></td>
</tr>
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<td>0.3 1.2 6.0</td>
</tr>
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</table>

Table 5.11: Means of the patient-paired differences in primary dose metrics in the anterior quadrants. The null hypothesis was a zero mean difference. Differences for which no observers showed a significant result are not listed.
### Mean paired difference

<table>
<thead>
<tr>
<th></th>
<th>Arm 2 – Ctrl</th>
<th>Arm 3 – Ctrl</th>
<th>Arm 4 – Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day-0</td>
<td>Day-30</td>
<td>Day-0</td>
</tr>
<tr>
<td>V100</td>
<td>NS</td>
<td>-2.5, -1.3, 0.0</td>
<td>NS</td>
</tr>
<tr>
<td>D90</td>
<td>-12.8, -7.0, -1.3</td>
<td>-9.8, -7.2, 1.8</td>
<td>-11.2, -5.7, -0.1</td>
</tr>
<tr>
<td>V150</td>
<td>NS</td>
<td>1.1, 3.6, 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>V200</td>
<td>NS</td>
<td>1.1, 3.6, 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>V90</td>
<td>NS</td>
<td>-12.8, -6.7, 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>D100</td>
<td>NS</td>
<td>-9.6, -5.0, -0.5</td>
<td>NS</td>
</tr>
<tr>
<td>V100</td>
<td>NS</td>
<td>-0.6, -0.3, -0.1</td>
<td>NS</td>
</tr>
<tr>
<td>D90</td>
<td>-9.6, -5.0, -0.5</td>
<td>-8.0, -4.2, -0.4</td>
<td>NS</td>
</tr>
<tr>
<td>V150</td>
<td>-7.6, -4.0, -0.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>V200</td>
<td>NS</td>
<td>-5.0, -2.8, -0.6</td>
<td>NS</td>
</tr>
<tr>
<td>V90</td>
<td>NS</td>
<td>-5.2, -2.6, -0.1</td>
<td>NS</td>
</tr>
<tr>
<td>D100</td>
<td>-13.4, -8.0, -1.5</td>
<td>-8.0, -4.2, -0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 5.12: Means of the patient-paired differences in primary dose metrics for the posterior quadrants.

The null hypothesis was a zero mean difference. Differences for which no observers showed a significant result are not listed.
5.3.5 Seed and Needle Utilization

The patterns of seed and needle utilization between the arms are shown in Table 5.13. All experimental arms used fewer seeds than the control-arm, as expected, since the mean activity per seed in these arms was higher. Arm-2 required the fewest seeds, a mean reduction of 26% relative to the control-arm. Arm-4 made the most efficient use of needles, using an average of 23% fewer than the controls.

<table>
<thead>
<tr>
<th>Arms</th>
<th>1 (Ctrl)</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean # seeds</td>
<td>122.8</td>
<td>90.9</td>
<td>102.1</td>
<td>93.5</td>
</tr>
<tr>
<td>Total 0.424U</td>
<td>122.8</td>
<td>-</td>
<td>51.4</td>
<td>32.1</td>
</tr>
<tr>
<td>0.6U</td>
<td>-</td>
<td>90.9</td>
<td>45.9</td>
<td>49.4</td>
</tr>
<tr>
<td>0.9U</td>
<td>-</td>
<td>-</td>
<td>4.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Mean # needles</td>
<td>25.3</td>
<td>20.4</td>
<td>21.4</td>
<td>19.5</td>
</tr>
<tr>
<td>Mean total activity (U)</td>
<td>51.9</td>
<td>54.5</td>
<td>53.6</td>
<td>53.9</td>
</tr>
</tbody>
</table>

Table 5.13: Seed and needle utilization per implant

5.4 Discussion

There is no definitive activity for PIPB. At the BCCA, 0.42U seeds have been used since the inception of the program, per the Seattle protocol\(^\text{77}\). However, other centres have different dosimetric goals, planning guidelines, and implant techniques\(^\text{218,228,229}\). Even within Canada there are distinct differences. In Edmonton, seeds of 0.5U are used in a modified peripheral loading scheme\(^\text{97}\). The decision to escalate seed activity there followed a study of different activities which found seed strengths in that range to maximize D90 while constraining V200 below 25% of their mPD\(^\text{219}\). A clinical evaluation of implants in this range was subsequently conducted to verify these findings\(^\text{230}\). In Quebec City an inverse-planning protocol is followed which uses high activity 0.76-0.84 U seeds, which seems to result in excellent outcomes and comparable toxicity\(^\text{217}\).

A number of planning studies\(^\text{89,230,231,232}\) have indicated that higher seed activities can be used to increase pre-implant coverage and D90 while keeping high dose volumes acceptably low. A study which looked at mixed activity plans of three activities suggested that such plans offered comparable coverage to 0.6U uniform activity implants\(^\text{231,233}\). As with all studies that use planned dosimetry as an endpoint, it is unclear whether the apparent benefits in pre-implant dosimetry translate into better post-implant outcomes.

This study did not propose changes to the BCCA’s dosimetric goals, but focused on investigating the potential of using high and mixed activity plans to accomplish them, using simulated post-implant metrics.
as an endpoint. There was no intention to maximize D90 in planning, or drive down V150 or V200. In fact, due to the narrow range of acceptable pre-implant dose metrics and margins in the current guidelines there was far less dosimetric variability between the arms in this study than is typical in the literature comparing plans of different activities. During planning, the occasional deviation from the guidelines was within the range traditionally tolerated. Where it was possible to better realize the aims of the planning guidelines by leveraging the flexibility of mixed activity seeds, this was done. For example, one of the principal benefits noted during treatment planning was the comparative ease with which the base plane could be covered in the mixed-activity arms by using 0.9U seeds at the distal tips of strands. This permitted regional increases of dose in this area without recourse to needles dedicated to this task, which would not have been clinically acceptable when the control was planned. As much as was possible, trade-offs in the planning of Arms 2-4 reflected clinical precedents. In Arm-4, needles were aggressively pruned from the plan in order to determine whether this resulted in less robust dosimetry than the more conventionally populated implants used in Arm-3.

Before continuing, it is worth discussing the impact of an important limitation of this study, namely that the freedom to optimize dose in the experimental treatment arms was inherently curtailed by the need to constrain their seeds to subsets of the low-activity seed positions. To what extent did the narrow palette of seed positions handicap the dosimetric quality of the experimental arms? Clearly, no experimental plan herein can be considered optimal under the circumstances. Better plans may well have existed in each case, and this includes the low activity arm. However, all treatment plans met the guideline requirements for dose-volume parameters, V150 dose shaping, and dose margin constraints. This is not a trivial standard of plan quality to meet, and as a result the similarity in treatment intention between arms herein far exceeds that in the literature. This was largely possible because of the atavistic preference for seed homogeneity in standard BCCA plans, reflecting the planning algorithm’s evolution from the Seattle protocol. Given the relatively even distribution of seed positions from which to choose, the constraints on the experimental arms in this study were probably not crippling.

The nature of the post-implant ‘simulation’ used in this study implicitly assumed that the effects of edema were identical between arms, despite differences in the number of needles from the clinical plan that actually induced the edema. It was also assumed that the oncologist would have behaved consistently during the implantation of each arm. It is conceivable that the use of higher activity seeds might have provoked physician anxiety about urethral or rectal doses, resulting in different steering patterns or use of unplanned seeds to cover perceived dose gaps. The impact of psychological variables was not controlled for by the methodology used in this study.

The robustness of loose-seed style implants to treatment uncertainties was evaluated in a comprehensive study by Beaulieu et al. In their study, the authors simulated seed misplacement and migration on
treatment plans using uniform activity plans in the range of 0.25-1.14U. Planning was performed using an in-house planning algorithm that aimed to achieve an mPD of 160 Gy. After the plans were created, a Monte Carlo simulation was applied to perturb the seed positions and simulate seed loss. These simulated prostate V100, D90 and D10 were compared as a function of seed activity. Despite adequate coverage in planning, the simulated post-implant V100 was found to decrease in proportion to activity after a threshold of about 0.9U. A similar trend was found in D90. Implants in the mid-range of activities (0.5-0.9U) had comparable coverage to plans below this range, even when seed loss was considered.

Interpreting this in the context of the BCCA program is challenging. In addition to differences in the prescribed mPD, Beaulieu et al.’s study used loose seeds, all of which were planned within the prostate capsule. The simulation parameters that informed their Monte Carlo algorithm were derived from post-implant distributions that reflected this planning paradigm, which is quite different from that of the BCCA. The clustering and stretching of seed trains modeled in their simulation is not applicable to strands, which move as a group when misplacement occurs. As a consequence of these factors, the results of their simulation may not pertain to BCCA plans.

Furthermore, recall that in Chapter 4, substantial changes in the post-implant seed cloud were evident during the resolution of edema, which affects the dose distribution. An important conclusion was that seed fixity depends on the environment in which the seed is deposited. The fixity of extraprostatic seeds, which account for ~40% of all seeds at the BCCA, may be more tenuous than those near the centre of the implant. Seeds implanted into the seminal vesicles were more likely to detach and migrate locally, whereas distant migrations out of the pelvis were seen primarily with strands implanted into the anterior base. The Monte Carlo simulations described by Beaulieu et al. neglected such factors, as well as the radial dependence of seed displacement during contraction. The use of actual post-implant seed distributions in the present study sidesteps all of the limitations of using a statistical model to incorporate misplacement and migration.

With respect to the uniform high activity plans (Arm-2), the results of this study differ from many reports in the literature which show that increasing seed activity tends to increase post-implant prostate V100 and D90. Relative to the clinical control (Arm-1), differences in D90 in Arm-2 were insignificant at day-30, and in fact were poorer than the control on day-0. One reason for this may be greater consistency in the planned dosimetry between arms in this study. In general, variations in pre-implant dosimetry between the arms in the studies reported in the literature, especially D90, are not described in detail.

For example, the randomized trial by Narayana et al. found that 0.76U seeds resulted in dosimetry superior to that achieved with 0.4U seeds. However, the ratio of the prescription dose volume to the CTV in their high activity arm was 17% greater than that of their low activity arm, and mean V200 was 30% greater (both in relative terms). Under such circumstances, it is not entirely surprising that post-implant...
coverage was better, but was it better because of the high activity seeds or the more generous treatment plans? The natural tendency for high activity implants to produce wider margins when urethral sparing is a major planning goal may be the driving force behind the relative success of high activity implants in other studies. This is not undesirable; indeed, the BCCA protocol deliberately espouses wide margins. However, studies such as this do not adequately answer whether high activity seeds can be used to achieve dose distributions that are equivalent to a low activity plan. One feature of this equivalence is dose conformity, which has generally been neglected as an endpoint. Although there is a paucity of data regarding the impact of dose conformity in prostate brachytherapy, greater normal tissue sparing is generally seen as an advantage in radiotherapy. In this study, the CI in the high activity arm was 5.3% greater than the low activity arm. This indicates that 0.6U seeds are capable of comparable dose conformity to 0.4U seeds.

No study to date has reported on the post-implant endpoints of mixed activity implants. In this study, the mixed activity arms generally had higher D90 and V100 values than the controls, while V150 was reduced. D90 increased by 3.4-7.2 Gy and V100 increased by 1.0-1.6% on Day-30. Like Arm-2, these arms were marginally less conformal than the control, with an average relative increase in the CI of 2.6-3.0%.

Because whole gland metrics may obscure geometrical shifts in dose distributions about the gland, quadrant analysis was also undertaken. Of specific interest was the anterior base, which is widely recognized as being challenging to adequately cover. In Chapter 1, a number of reasons were identified for this phenomenon. Tissue in this region is fibrous and difficult to maneuver needles in, causing issues like needle divergence. Poor TRUS visibility often results in the over-contouring of the gland in the anterior base, and a seed being inadvertently planned in what is actually the bladder or bladder wall. As was demonstrated in Chapter 4, these seeds are subsequently at greater risk of migrating into the bladder and being voided in urine.

The ability to increase seed activity at the distal tips of the strands in the mixed activity arms significantly rectified post-implant coverage in the ASQ. At day-30 the ASQ-V100 in the mixed activity arms increased from a mean of 72% in the control-arm to 75-77%. ASQ-D90 at this time point also rose by 7.4-10.6 Gy relative to the control, from 116 Gy to 123-126 Gy. There were associated increases in ASQ-V150 and ASQ-V200, but given the low baseline doses it seems unlikely that this will become a cause for clinical concern.

It could be argued that the reason for the traditionally poor ASQ coverage is the sanction on adjacent seeds in the planning guidelines, which artificially limits coverage in the base. However, even if permitted, as it is by other institutions, ‘doubling up’ of seeds to increase the ASQ dose is a poorer solution than using mixed activity for three reasons. The first reason is that it is simply more expensive. Second, for an equivalent needle depth, the more inferior seed of the pair would be further away from the base, and thus
Chapter 5 – Dosimetric outcomes of simulated mixed-activity implants

the seed activity would need to be higher to achieve a comparable effect. This would inevitably lead to higher central doses for the same coverage. Third, the impact of inter-seed attenuation is greatest in abutting seeds, as they each subtend a greater solid angle of the other’s steradian space. The TG-43 dose calculation is not sensitive to this, but research using Monte Carlo calculations has shown that the dosimetric impact of interposing seeds and calcifications can be significant \(^{179,235,236}\).

As the dosimetric planning constraints resulted in a roughly zero-sum game, the ASQ escalation in the mixed activity arms was offset by a reduction in high dose volumes in the inferior gland, notably the posterior inferior quadrant. However, this quadrant is typically well covered, and so this reduction is unlikely to be deleterious. At day-30, the control-arm had nearly complete coverage at the prescription level. PIQ-D90 = 222, PIQ-V150 = 90%, and a PIQ-V200 = 52%. In the mixed-activity arms, the PIQ-D90 decreased by 6.0-8.4 Gy, the PIQ-V150 by 1.4-3.9%, and the PIQ-V200 by 3.4-5.3%. The decrease in PIQ-V200 represented a relative reduction of 7-10%. Coverage at the prescription level was unaffected. The control dose in this quadrant was high with respect to historical averages \(^{93}\) in which PIQ-D90 and PIQ-V150 were closer to 200 Gy and 77% respectively. Given evidence that rectal hotspots are almost entirely due to dose margins in this quadrant \(^{226}\) the decline in these very high PIQ doses could be considered an improvement in implant quality.

With respect to the remaining quadrants, V100 was in almost all cases >95%, with D90>160 Gy. Significant decreases in PSQ-D90 occurred in all experimental arms for all observers. PSQ-V150 also fell in the mixed activity arms. In Arm-4, the PSQ-D90 fell by up to 10 Gy, and PSQ-V150 by up to 7%. However, these differences were only present at day-0. The only significant difference from the control at day-30 was a reduction of ~4% in PSQ-V150 in Arm-2. The AIQ was negligibly impacted. Only the AIQ-D100 in the experimental arms showed any significant differences from the control. Given the high baseline levels of coverage in the control-arm in these regions, these reductions are not expected to impact tumour control.

Urethral dose metrics in the mixed-activity arms were significantly higher than the controls, typically due to the dose intensification that was possible in the anterior base. UD10 increased by 6.8-8.7 Gy, a relative gain of 4-5% over the control. UD30 increased by 2.8-3.0 Gy, a relative gain of 2%, but only in Arm-3. Unfortunately, day-30 urethral dosimetry could not be evaluated due to the absence of a catheter. This suggests that mixed-activity planners should exercise caution in using high activity sources too medially in the ASQ. However, the increase in urethral dose in the experimental arms did not result in any patient who did not already have a UD10>150%mPD or UD30>130%mPD (3 pts.) from crossing these thresholds, which are the targets recommended in TG-137. The maximum increase in UD10 was 53 Gy in Arm-2. The corresponding maximum increases were 21 Gy in Arm-3, and 28 Gy in Arm-4. From a toxicity perspective, the impact of these changes is difficult to gauge quantitatively, as there is no evidence of a link.
between urethral dosimetry and toxicity in modern brachytherapy series\textsuperscript{124}. Nonetheless, it is a result that will need to be considered in the development of a clinical mixed-activity planning protocol.

In comparison, rectal dosimetry is well correlated to morbidity, with RV100 being repeatedly implicated in the risk of rectal bleeding\textsuperscript{237,238,239,240,241}. The conclusions of these reports have been corroborated by BCCA data, which found that RV100 was significantly correlated with late RTOG toxicity\textsuperscript{241}. In this study, the most concerning feature in the experimental arms was the rise in RV100 in Arm-2, which was a mean of 0.18 cm\textsuperscript{3} greater than the control at day-30. This corresponds to a relative increase of 21%. This is somewhat contrary to the experience of Masucci et al.\textsuperscript{172}, who found that rectal dose metrics decreased significantly when transitioning from 0.6U to 0.8U seed implants. However, in their study rectal doses were much higher in general, and the extent to which planned dose margins along the posterior of the gland differed between their planning arms is not explicit in their report.

It is also possible that the higher rectal doses in Arm-2 reflect the aforementioned scarcity of implantable posteromedial needle positions. Institutions that use high activity seeds may prefer to configure their implants such that the minimum distance between any seed and the rectal wall is greater, so that dose at the rectal interface from such seeds is less sensitive to misplacement. The limitations on seed placement in our study precluded an investigation into the merits of this approach. A potential consequence of treating at greater distances may be that to increase V150, as the seed sits more centrally, and a relatively greater strength would be necessary to deliver a comparable dose at the periphery. Such a trade-off may explain the tendency to greater total implanted strength in high-strength protocols. What is needed is evidence that insufficient seed separation from the posterior aspect of the gland is associated with higher post-implant rectal dosimetry in implants with comparable pre-planned dose distributions. If this were found to be true, it may signify the need for separation to be considered as an independent constraint in a future high or mixed activity planning protocol.

Needle inflicted trauma to the prostate has been implicated in the risk of urinary toxicity and erectile dysfunction\textsuperscript{124,148,242,243}. This study has shown that by using mixed activity implants, the number of needles could be reduced by \textasciitilde25\% while maintaining or improving dosimetric quality. Plans with fewer needles also take less time to implant. This implies a shorter duration of anaesthesia and subsequent recovery for the patient.

Seeds are one of the largest components of the cost of PIPB. At \$30-40 per seed, Arm-2 and Arm-4 represent a cost savings of approximately \$1200 per implant relative to the current clinical standard, as seed costs are independent of strength at this time. The BCCA treats nearly 500 patients per year, and the implementation of mixed activity implants could foreseeably save the province \textasciitilde\$600,000 annually. There are also likely to be significant cost savings associated with less time spent in the OR.
5.4.1 Conclusions

Mixed-activity implants are a better method for reducing needle counts and covering the ASQ than high-activity implants. In this study, high and mixed-activity implants were planned using a subset of the seed positions used in the low activity implants of a cohort of patients. Each arm of this study conformed to the narrow range of acceptable dosimetric parameters and constraints of the traditional low-activity planning guidelines used at BCCA. Using algorithms developed as a part of this thesis work, the outcomes of the high and mixed activity implants were then evaluated by appropriately reassigning the activities of these seeds in the clinical post-implant seed distributions. This controlled for many of the uncertainties associated with the misplacement and migration of seeds during implantation.

High-activity (0.6U) implants provided comparable target coverage to low activity implants, but had the greatest variability in dosimetry, and significantly higher rectal dosimetry. Mixed-activity implants were able to significantly improve dosimetry by enhancing coverage of the anterior base, and reducing hotspots in the posteroinferior aspect of the gland. Urethral doses in mixed-activity implants increased significantly, primarily as a consequence of higher activity seeds in the anterior base, where the urethra enters the prostate. However, in comparison to the increases seen in rectal doses for the high-activity arm, the absolute impact on the urethra was minor. Both high and mixed-activity arms managed to reduce needle counts by ~25%. Limiting the experimental plans to subsets of pre-defined seed and needle coordinates was necessary to accomplish the post-implant simulations herein. Both high and mixed activity implants designed without these constraints may not have the same limitations. The results support advancing mixed-activity methodology to clinical trials, for which no such constraint will be necessary, and the full flexibility of the technique can be leveraged to further accentuate the identified benefits.
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6 Conclusions

6.1 Contributions and Recommendations

Post-implant dosimetry is a critical assay of implant quality, and forms the basis for comparing the relative effectiveness of different techniques. In Chapter 2, a method was developed to quickly and accurately determine the ultimate location, in the post-implant CT dataset, of each planned seed. The traditional difficulty in this process has been that delivery uncertainties conspire to distort the reproduction of the planned seed distribution in the patient, diminishing the sensitivity and specificity of seed location as an identifying attribute. To address this, the algorithm presented uses a multi-stage approach in which likely strands are first segmented using the relatively low-noise criterion of inter-seed spacing. The likely strand paths then inform a general-purpose quadratic assignment algorithm, which dramatically improves the accuracy of the final result. Using the algorithm, the mean assignment accuracy on a set of 70 post-implant cases rose from 85% (when only seed position was used as a matching criterion) to 98%.

An interface for plan reconstruction has been deployed at the BCCA for the purpose of verifying the positions of the segmented seeds. As described in Chapter 2, organizing the seed cloud into a coherent set of strands, each with the correct seed count and relative position, is a strong indicator that all the seeds have been found, and that they have been found in the correct locations. It is a valuable tool for distinguishing calcifications, which often masquerade as seeds in CT images, and for resolving the ambiguity between seeds with a large image artifact and true seed clusters. It is very unlikely that a seed segmentation error will not become evident during the process of plan reconstruction.

Traditionally, seed segmentation and verification has been the task of a medical physicist. However, it is the radiation therapist who is typically present during the procedure, and who is responsible for recording seed use, delivery complications, and any intraoperative changes to the plan. This makes them better suited to the task of plan reconstruction from a workflow perspective. The difficulty in delegating the seed segmentation has been that it does not ameliorate the time necessary to perform the final physics ‘check’, which still requires examining individual seeds. However, using plan reconstruction, this check can be streamlined by validating the overall reconstruction rather than the segmentation of individual seeds. This improves the efficiency of PIPB quality assurance and reduces the likelihood of dosimetric errors.

Reconstructed plans also allow the pose of strands and their relative positions with respect to the contoured target to be easily examined. This facilitates an understanding for how intraoperative uncertainties affect the accuracy of strand placement. Plan reconstruction provides a hitherto unavailable opportunity for oncologists to appreciate the consequences of needle deflection and gland deformation, and to refine their technique accordingly. This author recommends the development of QA metrics related to how accurately the delivered seed distribution matched what was planned. This would isolate the technical factors
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associated with reproducing the planned seed arrangement from contouring uncertainty, giving oncologists more specific feedback. An authentic replication of the planned seed distribution in the patient coupled with poor dose metrics may indicate that the contours, rather than the implant technique, require rectification.

In Chapter 3, a method for determining the orientation of implanted seeds was described, in order to enable a 2D calculation of the dose distribution as recommended by the AAPM. This was based on the curvature of cubic splines fit to each strand, as identified by plan reconstruction. Using this technique, it was shown that differences on the order of 2% could be expected in the primary dose metrics with respect to when the 1D calculation is used. This suggests that the alignment of strands in stranded implants does not substantially impact common measures of implant quality, at least for BCCA implants as they are currently performed.

However, the finding that strands are pitched at a mean of approximately $21\pm10^\circ$ from the coronal plane may be cause for concern. Recall that the German study which looked at the geometric distribution of high dose regions in the rectal wall identified the apical seeds in the posterior strands as being the principal contributors to D0.1cc and D2cc. Moreover, those authors reported a mean pitch of $11\pm9^\circ$, only half of what was measured at the BCCA, and their implant technique avoided extraprostatic seeds in the apex. This may be because the large implant margins at the BCCA require greater probe angles in order to avoid the pubic arch during needle insertion, especially in patients with large glands. Given the association between the apical seeds and rectal doses, the relatively high magnitudes of strand pitch, and the use of extraprostatic seeds at the apex, BCCA patients may be at greater risk of rectal complications than patients at other centres. This becomes especially consequential if there is inferior migration of the posterior strands. Mixed-activity implants offer a potential solution. By using higher activity seeds in the anterolateral aspects of the implant, needles can be brought medially, mitigating interference issues and the need for high probe angles. In addition, concurrently de-escalating the activity in the most apical seeds of the posterior strands may help to mitigate the consequences of any migration.

Further motivation for mixed-activity implants was presented in Chapter 4, where the sensitivity of the implant to seed loss and migration was shown to be region specific. Seeds implanted near the bladder wall and periurethral zones were at greater risk of distant migration. Strands that transgressed the bladder occasionally lost multiple seeds by day-30, underscoring the importance of mitigating this phenomenon in stranded implants. The results of this thesis suggest that seed fixity at the BCCA would be significantly improved if anteromedial needles could be planned at more conservative depths. Mixed-activity implants offer this possibility, using high activity seeds at the tips of these strands to negotiate coverage of the anterior base.
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The measured patterns of stranded seed displacement during the resolution of edema were found to be in rough agreement with the existing empirical models for prostate contraction. A TPS-based transformation, informed by statistical descriptors of seed displacements, was developed in order to distinguish whether systematic displacements were occurring. Applying the transform to day-0 seed positions shifted them 15% closer to their positions at day-30, on average. This transform was 2 – 4 % better in this respect than the isotropic or anisotropic contraction models, although it was the similarities rather than the differences which were noteworthy. Nonetheless, the majority of the displacement could not be accounted for, even under a broad range of edema magnitudes and decay parameters. No obvious difference was seen between the dynamics of stranded seeds and the small collection of loose seeds that were used.

Dosimetric accuracy on a per-voxel basis also improved after the TPS transform, with approximately 10% fewer voxels in the target region differing from their day-30 doses by more than 10% relative to the day-0 distribution. Total dose volumes arising from the transformed day-0 seed positions were also markedly similar to the corresponding volumes at day-30. However, dose metrics evaluated on the correspondingly transformed day-0 prostate contours did not result in a better estimation of the day-30 dose metrics. This may be due to inhomogeneous distributions of edema in the prostate, or simply inconsistencies in contouring. In any case, the possibility of a robust method of projecting dosimetric results from day-0 data remains an open question.

It remains uncertain why seeds which appear to be at the same relative position from the centre of the prostate in different patients exhibit such marked differences in their directions of displacement. Possible explanations for this phenomenon are registration errors of the gland between time-points, presence of the catheter at day-0, patient specific anisotropy, asynchronous seed displacement due to patient movement, or some combination thereof. Better integration of multimodality imaging (i.e. MR-CT) may help to resolve this in the future. Such image fusions were not pursued in this thesis because the errors accrued by the tools currently available to perform this process were expected to blunt any of the benefits of greater visibility. Further clarification will thus require more accurate methods of MR-CT fusion, or advances in MR seed detection such as those proposed by the group at MD Anderson\textsuperscript{244,245}.

Despite these sources of uncertainty, the TPS transformation was in surprisingly broad agreement with the displacement predicted by the independently derived prostate contraction models. Without downplaying the enormous variability of individual seeds, the overall trend in stranded seed displacement in the first month seems to be consistent the expected contraction of the prostate as independently reported in the literature. Since there is no comparable evidence that loose seeds possess greater tenacity at the time of this writing, this study supports the continued use of stranded seed products; the benefits of reduced embolism appear at this juncture to outweigh the risks of asynchronous migration. The main concern associated with
stranded implants, the risk of whole strand migration into the bladder, may be mitigated through a mixed-activity approach as has been described.

In the previous chapter, a treatment planning study was presented which investigated the robustness of mixed-activity implants to treatment uncertainties. The main purpose of this was to establish whether mixed activity implants were capable of achieving dose distributions comparable to traditional low-activity seeds. In this respect, mixed-activity implants were found to improve the coverage of the anterior base, moderate the dose intensity in the posterior apex, and reduce the number of needles necessary for treatment. The only observed drawback was an increase in urethral dose, which was largely a consequence of meeting coverage goals in the anterior base. The clinical significance of these dosimetric trade-offs is unclear, but the general trends are promising. There is also good evidence to suggest that the reduction in the number of needles used will lessen urinary toxicity, without the risk of escalation in rectal doses that may occur if uniform high activity plans are used to reduce needle counts.

Due to the limitations in the planning of the experimental arms that was necessary to perform the implant simulation, these results likely understate the potential of high or mixed-activity dosimetric quality. It is the opinion of the author that the ability to freely choose needle positions and seed placements will result in substantially better results that could be shown under the constraints of this thesis.

6.2 Adjunct and Future Work

6.2.1 Clinical Trial of Mixed-activity Implants

A clinical trial of mixed-activity implants is the obvious continuation of this work. As suggested above, its focus should be to leverage high activity seeds to mitigate the risk of strand loss associated with bladder perforation, or seed deposition in the periurethral tissue. Improved fixity, rather than better dose conformity in planning, should be the guiding principle of protocol development. To contain high rectal dose volumes, the posterior aspect of the gland should remain the province of low activity seeds except in the base, where the strands diverge from the course of the rectum. Another approach might be to use higher strength seeds at greater separation from the rectal wall. Selecting between such options will require further study.

A method for performing the pre-implant quality assurance of mixed-activity needles is the subject of ongoing research. The current practice is to acquire an x-ray image of the needle tray and verify that seeds are correctly loaded. It is assumed that the loaded seeds come from the same batch, whose activity is assayed at the radiopharmacy. However, in a mixed-activity approach it may be deemed necessary to verify the distribution of seed activities within each needle. This could be based on a combination of a
collimating device to reduce inter-seed interference, and an x-ray detector to acquire autoradiographs for verification.

6.2.2 TRUS-CT Registration Using Plan Reconstruction

A consistent limitation in this thesis and in post-implant dosimetry in general is the challenge in accurately delineating the prostate gland in post-implant CT. Although MR imaging offers better visualization, its cost is difficult to justify for the purposes of routine post-treatment verification, and the process of CT-MR fusion is subject to its own significant variability. Researchers at the BCCA are currently investigating methods of transposing contours from intraoperative TRUS to the post-implant CT, using the seed correspondences elicited by plan reconstruction as registration landmarks. As prostate visibility is superior in TRUS, this method is hypothesized to reduce observer effects in post-implant quality assurance. A warping algorithm developed for automatic prostate segmentation is being explored to account for the probe-induced deformation $^{79,80}$.

6.2.3 Impact of Intraoperatively Planned Seeds

BCCA oncologists routinely utilize one to five seeds to augment perceived holes in the seed distribution at the conclusion of the procedure. These seeds are placed without dosimetric feedback, under fluoroscopic guidance. Plan reconstruction was used by BCCA researchers to investigate the patterns of use, and impact of these seeds on the post-implant dose distribution of 70 patients. The author provided technical assistance with the software and training. Extra seeds were found to be used in 83% of the implants. In the majority of cases, all five seeds were used, usually to rectify coverage in the anterior base. On average, the use of these seeds was found to increase V100 and D90 in the ASQ by 9% and 11 Gy respectively. Whole prostate V100 increased by 3.3%, and D90 increased by 9.1 Gy. Mean urethral doses increased by a mean of 5.8 Gy, but UV150 as well as all rectal dose metrics were negligibly impacted. This work underscores the difficulty in implanting the anterior base, and sets the bar for any future implementation of intraoperative plan adaptation using real-time dosimetry.
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