Conformal Heating of the Prostate for the Treatment of Localized Cancer using MRI-Guided Transurethral Ultrasound

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Medical Biophysics
University of Toronto

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Abstract

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Prostate cancer is the most prevalent cancer and the third-leading cause of cancer-related death among men in the developed world, with the number of cases expected to double within the next 15 years. Conventional therapies offer good control of local disease but are associated with high complication rates reducing long-term health-related quality-of-life significantly.

MRI-guided transurethral ultrasound therapy has emerged as an attractive, minimally-invasive alternative for the treatment of localized prostate cancer, where the entire gland is heated to temperatures sufficient to cause irreversible thermal coagulation. A device inserted in the urethra uses multiple ultrasound transducers to produce directional heating patterns directly in the prostate. Adjusting the ultrasound power, frequency and device rotation rate enables high spatial control of the thermal lesion. MRI provides information essential to the accurate targeting of the prostate; anatomical images for device positioning and treatment planning, and quantitative temperature measurements within the prostate to compensate for dynamic tissue changes, using feedback control.

This thesis develops a complete treatment delivery strategy for producing conformal regions of thermal coagulation shaped to whole-gland prostate volumes, while limiting the
thermal impact to the surrounding important anatomy. First, acoustic and thermal simulations incorporating a novel temperature feedback controller were used to model and shape regions of coagulation to human prostate geometries with a high degree of accuracy. Second, treatment delivery strategies were developed and simulated to reduce thermal injury to the surrounding anatomy, below the threshold for sustained damage. Third, experiments in tissue-mimicking gel phantoms confirmed the predictive accuracy of the simulations and the feasibility of producing conformal volumes of coagulation using transurethral ultrasound devices and MRI-temperature feedback. This work forms the basis of clinical treatment delivery methods and supports the use of the simulations as a planning tool to enhance the inherent compromise between safety and efficacy on a patient-specific basis.
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1 Introduction and Background

1.1 Prostate and Cancer

1.1.1 Prostate Anatomy and Physiology

The prostate gland is a walnut-sized organ that surrounds the urethra and is located between the bladder (prostate base) and the penile bulb (prostate apex). It is mainly comprised of three distinct zones: the transition zone (surrounds the urethra from the bladder to the colliculus near mid-prostate), the central zone (forming a funnel around the transition zone and containing the ejaculatory ducts), and the peripheral zone (the largest zone including the peripheral sections of the prostate, the apex and the regions neighboring the rectum). The prostate gland is part of the male reproductive system and its main function is to combine seminal fluid, sperm and nutrients to create semen which it then expels with pulsating contractions during ejaculation. While the prostate is not considered to be a vital gland, it is in close proximity to many organs and anatomical structures that are essential in maintaining quality of life: internal urethral sphincter (involuntary control) contained at the junction of the urethra with the urinary bladder (bladder neck), external urethral sphincter (voluntary control) located in the urogenital diaphragm (UGD), rectum, neurovascular bundles (NVB) and pelvic bone, as illustrated in Figure 1 [Kirby 1997]. When treating prostatic diseases, the major challenge often lies in avoiding damage to the sensitive surrounding anatomy.
Figure 1: Anatomical diagram of the prostate and surrounding important structures [Kirby 1997]. The pelvic bone is not shown. The major challenge in treating the prostate is to avoid damage to the surrounding structures, which could affect the patient’s quality of life.

1.1.2 Prostate Cancer

The most prevalent conditions affecting the prostate are benign prostatic hyperplasia (BPH), a non-life-threatening enlargement of the prostate which usually develops in the transition zone, and prostate cancer which commonly originates in the peripheral zone [Kirby 1997, Grignon and Sakr 1994]. The incidence of both of these conditions rises significantly with age [Canadian Cancer Society 2010]. The treatment of BPH is palliative in nature, thus allowing simple approaches aimed at reducing prostate volume to be applied successfully and generally without long-term complications [Gurunadha et al 2002]. The treatment of localized prostate cancer, on the other hand, is much more challenging because accurate targeting of the entire prostate gland is required while limiting damage to the surrounding anatomy.

Prostate cancer is the most prevalent cancer and the third-leading cause of cancer-related death among men in the developed world [Parkin et al 2005], with an estimated 24,600 new cases and 4,300 deaths in Canada in 2010 and the number of cases expected to double within the next 15 years [Canadian Cancer Society 2010]. Furthermore, prostate cancer is the most commonly diagnosed and second-leading cause of cancer related death among men in the
United States of America with an estimated 217,730 new cases and 32,050 deaths in 2010 [American Cancer Society 2010]. In Canada, prostate cancer is the most frequently diagnosed cancer, ahead of lung, breast and colorectal cancer [Canadian Cancer Society 2010].

Prostate cancer is usually a very slow-growing, indolent disease, and even though it is extremely widespread, only approximately 20% of those affected eventually die from it [Canadian Cancer Society 2010]. The use of the prostate-specific antigen (PSA)* test as a screening tool over the last 20 years has decreased the average age and increased the proportion of men diagnosed with low-grade, small-volume, localized prostate cancer [Cooperberg et al 2007, Neutel et al 2007]. While the PSA test is quite sensitive to prostate cancer, its specificity is relatively low and it cannot discriminate between the life-threatening and slow-growing forms of the disease [Hammerer et al 2002].

As a result, prostate cancer is overtreated; many men that undergo treatment for prostate cancer do not actually benefit from it, because they would have never developed symptomatic disease in their lifetime. Over-diagnosis and subsequent overtreatment of prostate cancer would be acceptable, although costly, if treatments had no morbidity. Since conventional prostate cancer therapies are associated with high complication rates affecting long-term health-related quality-of-life, patients and clinicians face the dilemma of how to manage the disease: whether or not to treat, when to treat and how to treat.

* Prostate-specific-antigen (PSA) is a glycoprotein protease secreted by the prostate to liquefy semen. About 0.1% of the total volume of PSA produced is absorbed across the basal cell layer and basement membrane resulting in normal blood serum levels of ≤ 4 ng/ml. Prostatic diseases, particularly prostate cancer, damage the basal cell layer or basement membrane, increasing the leakage of PSA into the bloodstream. [Kirby 1997]
1.1.3 Prostate Cancer Management

Over 90% of all prostate cancers are discovered in the local and regional states [American Cancer Society 2010], where the disease usually follows an indolent course; however, more than 90% of these low- to intermediate-risk patients elect to undergo radical treatment [Cooperberg et al 2004]. Considering the substantial side-effects and complications that commonly arise from conventional whole-gland prostate cancer treatments, patient quality of life can be worse after treatment. Specifically, the most common prostate cancer treatments, radical prostatectomy (surgical removal of the gland) and external beam radiation therapy (EBRT), provide good outcomes in terms of local disease control (fifteen-year disease specific survival rate of 90% [Tewari et al 2006]), but are associated with high complication rates affecting long-term sexual, urinary and bowel function, which can reduce the patient’s quality of life significantly [Potosky et al 2004]. Results from the Prostate Cancer Outcomes Study (PCOS), designed to prospectively assess the long-term quality-of-life outcomes for a large, diverse sample of men, showed that sexual†, urinary‡ and bowel§ dysfunction were prevalent five-years after treatment in, respectively, 79%, 16% and 11% of men treated with radical prostatectomy, and 64%, 4% and 20% of men treated with EBRT, as discussed in more detail in Table 1 [Potosky et al 2004]. Furthermore, with more than 80% of the new prostate cancer cases occurring in men over 60 years old [Canadian Cancer Society 2010], the impact of highly invasive radical prostatectomy or the burden of radiation therapy can be too great for a substantial portion of the target treatment population. While these conventional therapies continue to hold an important role in

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† Defined here as erection insufficient for intercourse.
‡ Defined here as having urinary leaks ≥ 2 times per day.
§ Defined here as painful haemorrhoids.
the management of prostate cancer (for example for high-risk cancers) due to their effectiveness and well-established long-term survival rates [Tewari et al 2006, Brenner and Arndt 2005, Zietman et al 2004], a variety of modern radiation and minimally-invasive surgical approaches are being developed, aimed at improving the risk-benefit ratio of their conventional counterparts.

Table 1: Comparison of 5-year Prostate Cancer Outcomes Study survey responders on individual urinary, bowel and sexual domain items [Potosky et al 2004]. Percentages adjusted for treatment propensity scores, age at diagnosis, baseline function, race/ethnicity, comorbidity, and educational level.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Radical prostatectomy (n = 901)</th>
<th>EBRT (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No control or frequent leaks</td>
<td>15.3 %</td>
<td>4.1 %</td>
</tr>
<tr>
<td>Leaks ≥ 2 times per day</td>
<td>16.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Wears any pads to stay dry</td>
<td>28.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Bothered by dripping or leaking urine</td>
<td>14.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Bowell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23.9</td>
<td>28.8</td>
</tr>
<tr>
<td>Bowel urgency</td>
<td>19.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Painful hemorrhoids</td>
<td>10.2</td>
<td>19.6</td>
</tr>
<tr>
<td>Bothered by frequent bowel movement to pain, or urgency</td>
<td>4.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Sexual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erection insufficient for intercourse</td>
<td>79.3</td>
<td>63.5</td>
</tr>
<tr>
<td>Bothered by sexual dysfunction</td>
<td>46.7</td>
<td>44.6</td>
</tr>
</tbody>
</table>

The most established of these techniques is brachytherapy which, similarly to EBRT, uses radiation to kill cancerous cells. The destructive energy, however, is delivered to the prostate via multiple permanent or temporary radioactive seeds implanted under image-guidance [Stock et al 1995, Ménard et al 2004]. Instead of delivering radiation to the prostate from outside the patient’s body, as in EBRT, brachytherapy aims to treat the prostate from the inside, thereby allowing an increased delivery of radiation dose to the prostate while maintaining similar or lower levels of radiation to the surrounding normal anatomy. While it is difficult to compare directly the outcomes and complications rates of brachytherapy (and other modern
treatment alternatives) with those of surgery and radiotherapy due to the lack of prospective randomized studies [Wilt et al 2008, Lotan 2010], brachytherapy has shown to provide good disease control (ten-year disease specific survival rate of 90% [Potters et al 2005, Beyer et al 2005, Gómez-Iturriaga Piña et al 2010]), though associated with significant sexual, urinary and bowel dysfunction [Stone and Stock 2002, Miller et al 2005, Gómez-Iturriaga Piña et al 2010]. One study showed that sexual and urinary side-effects were more prevalent in patients treated using brachytherapy compared to those with open radical prostatectomy, although the study was not randomized, it was from a single institution and there were significant baseline differences between the treatment groups [Malcom et al 2010].

One of the primary concerns while delivering radiation to the prostate using conventional EBRT is organ motion, both intra- and inter-fraction (during and between individual radiation treatments). Because the prostate may move relative to its position on treatment planning images, conventional EBRT uses 10 mm safety or treatment margins, meaning that it aims to treat 10 mm beyond the planned target volume (the prostate) [Cheung et al 2005, Ullman et al 2006]. If organ motion occurs, not only does the dose delivered to the prostate decrease, but the dose to the surrounding normal anatomy increases. In fact, EBRT has been associated with increased risk of bladder and rectal cancer, with treatment margins and organ motion likely being significant contributors [Nieder et al 2008]. Furthermore, with the development of increasingly conformal radiotherapy techniques, the accurate localization and targeting of the prostate becomes essential. In an attempt to account for organ motion and improve treatment outcome, radiation oncologists are developing a hypofractionated accelerated radiotherapy approach which combines EBRT with daily image guidance using gold seed fiducials implanted in the prostate [Cheung et al 2005, Tang et al 2008]. First, a hypofractionated radiation scheme aims to maintain bio-equivalent tumour doses with decreased treatment visits and complications [Martin et al 2007]. Second, organ motion is measured and
corrected using electronic portal imaging, which enables the accurate localization of the prostate with high reproducibility between observers due to the presence of the gold, radio-opaque fiducials markers [Ullman et al. 2006]. Inter-fraction motion is accounted for by imaging the prostate and adjusting the treatment plan prior to the delivery of each radiation fraction. Intra-fraction motion, respiratory-induced and absolute change in prostate position before and after each fraction as characterized over nine days of treatment, is accounted for using treatment margins which were reduced from 10 to 4 mm in a clinical trial of this technique at Sunnybrook Health Sciences Centre [Cheung et al. 2005]. While the trials are still ongoing, early results suggest the novel technique seems feasible and well tolerated [Tang et al. 2008]. Even though not all sources of intra-fraction motion were considered, for example from the passing of gas, methods to automatically detect organ motion and improve offline adaptive approaches to intra-fraction motion correction are in development [Prakash et al. 2008]. The increasingly useful role of image-guidance for adaptive treatment planning and therapeutic assessment, most notably by magnetic resonance imaging (MRI) [Ménard et al. 2001, Haider et al. 2008], will ultimately result in the individualization of radiation therapy for improved benefit and reduced risk.

In recent years, surgical techniques for the prostate have become less invasive with the aim of reducing blood loss during surgery, complications after treatment and general trauma and scarring to the patient. Today, robot-assisted laparoscopic prostatectomy using the da Vinci® robot is widespread (especially in the United States of America) [da Vinci Prostatectomy 2010]. While early studies showed reduced sexual and urinary complications using this minimally-invasive surgical approach [Kaul et al. 2005], more recent studies fail to demonstrate any benefit compared to open radical prostatectomy [Malcom et al. 2010].

Despite modern advances in radiation and minimally-invasive surgical techniques, complication rates affecting long-term health-related quality-of-life remain high. Additionally, patients who experience cancer recurrence after having surgery or radiation therapy cannot, in
general, be re-treated using these same approaches (partly motivating the initial decision for radical treatment) and, thus, alternative salvage therapies are required. There is still, therefore, strong motivation to develop a treatment for localized prostate cancer that can provide better or similar outcomes to conventional therapies with wider applicability and reduced complications in order to maintain good patient quality-of-life. Furthermore, less invasive methods or more conservative management approaches aimed at treating low- and intermediate-risk prostate cancer with fewer complications would have a significant impact on patient care.

Cryotherapy, the destruction of tissue through extreme freezing, offers a minimally-invasive alternative to surgery or radiotherapy, where a radical or conservative approach may be considered due to the possibility of re-treatment, if necessary. First proposed for the treatment of prostate cancer in the 1960’s [Gonder et al 1964], cryotherapy has experienced renewed interest due to increased understanding of cryo-biology, as well as the advanced development of treatment devices and image guidance technologies (most notably transrectal ultrasound imaging). Using multiple needle-like probes inserted in the prostate via perineal templates similar to those in brachytherapy, a frozen volume is shaped to conform to the prostate in an attempt to spare the surrounding anatomy from damage. Similarly to brachytherapy, it is difficult to compare cryotherapy with other localized prostate treatments due to the lack of randomized studies [Wilt et al 2008]. Some early- and intermediate-term clinical data show, however, that cryotherapy is equally or less effective than surgery and radiotherapy, with increased complication rates (particularly sexual impotence) [Long et al 2001, Bahn et al 2002, Parker et al 2009, Malcom et al 2010]. The limited clinical success of cryotherapy may be due in part to the complicated biology behind this therapeutic approach, where tissue injury depends on fast cooling to a lethal temperature (-40°C to -50°C) followed by slow thawing and subsequent repetition of the freeze-thaw cycle [Theodorescu 2004]. Furthermore, the cooling
and thawing rates are additional critical variables affecting cell kill, with the fastest cooling and slowest thawing rates providing greater damage to the cells [Theodorescu 2004].

While researchers are discovering new ways to treat prostate cancer with fewer complications, clinicians are revisiting the traditional approach to prostate cancer care. Watchful waiting and active surveillance are prostate cancer management schemes which aim to control the disease effectively in low- and intermediate-risk patients, while avoiding unnecessary widespread radical intervention and associated morbidity. Both approaches are similar in that patients diagnosed with favorable tumour characteristics are not immediately treated but instead closely monitored for disease progression.

The aim of watchful waiting is to initially avoid treatment and provide palliative intervention based on symptomatic progression. Since the intent is not necessarily to cure the patient from prostate cancer, this management approach is usually intended for older patients with shorter life expectancies (> 70 years old, < 15 years life expectancy) [Parker 2004]. Watchful waiting, in essence, relies on the fact that men with low-grade prostate cancers have a small risk of dying from prostate cancer within 15 to 20 years of diagnosis [Albertsen et al 2005]. However, a randomized trial from the Scandinavian Prostatic Cancer Group Study comparing radical prostatectomy with watchful waiting showed that, respectively, 12.5% and 17.9% of men died of prostate cancer, and 19.3% and 26% of men were diagnosed with distant metastases, 12 years after treatment [Bill-Axelson et al 2008]. Furthermore, quality-of-life data were collected from a subset of these patients, and, after 4 years, those managed using watchful waiting were more anxious and depressed and had a worse sense of well-being and self-assessed quality-of-life compared to the men treated with radical prostatectomy [Johansson et al 2009].

Active surveillance, first formally described in 2001 by Choo and his colleagues at Sunnybrook Health Sciences Centre, aims to provide an individualized treatment, selecting for curative therapy only men with significant cancers as determined based on evidence of disease
progression (serum PSA concentrations and repeat biopsies) [Choo et al 2001]. While most men diagnosed with favorable-risk prostate cancer never experience clinical manifestations of the disease, a subset of patients are at risk due to either the presence of higher-grade disease not apparent at diagnosis or progression of the disease over time to a more aggressive phenotype. Active surveillance is distinguished from watchful waiting in that instead of providing palliative treatment to men once they show symptoms of progressive disease, it closely monitors patients and intervenes with early, curative (radical) treatment in men with signs or evidence of disease progression. Active surveillance takes advantage of the indolent nature of prostate cancer to incorporate into patient management a period of initial observation, attempting to identify at-risk patients using close follow-up. The management approach of active surveillance with selected delayed intervention may offer low- and intermediate-risk patients a good compromise between treatment risk and benefit [Klotz et al 2010]. Faced with cancer, however, the majority of these men still elect to undergo radical treatment [Cooperberg et al 2004].

Focal ablative therapy, although controversial [Scardino 2009], addresses the overtreatment of indolent cancers and reduced quality-of-life, while offering an immediate therapeutic benefit to the patient. Similar to a lumpectomy versus a mastectomy for breast cancer, focal ablative therapy aims to treat only the sectors containing cancer in the prostate, thereby reducing the treatment volume and decreasing the risk of damaging nearby surrounding anatomy. While accurate spatial diagnosis of prostate cancer and the multi-focus nature of the disease remain critical challenges, up to 33% of radical prostatectomy patients have shown to be good candidates for focal therapy, having unilateral, low-grade, organ-confined tumours on final pathology [Jayram and Eggener 2009, Davis et al 2010]. In 2007, an international task force on prostate cancer described a good focal therapy modality as one which 1) shows pre-clinical evidence of tumouricidal activity throughout the entire target zone, 2) allows real-time treatment monitoring, 3) accesses the prostate percutaneously, or via the rectum or urethra, 4) affects only
a dominant tumour focus, causing minimal alteration of structures essential for sexual, urinary and bowel function, 5) not prohibitively expensive, 6) allows re-treatment and 7) allows subsequent whole gland therapy, such as surgery or radiation without excess morbidity. They also highlighted as good candidates for focal therapy, among others, high-intensity ultrasound, cyrotherapy and radio-frequency (RF) ablation.

High-intensity ultrasound therapy (using transrectal or transurethral devices) is of particular interest for the treatment of prostate cancer because it can heat and thermally coagulate precise volumes of tissue under image-guidance and temperature feedback control. This minimally-invasive approach offers the flexibility to be used as a radical treatment alternative to conventional prostate therapy, or as a treatment tool in the conservative management of the prostate within the framework of focal therapy or active surveillance. Ultrasound therapy and RF ablation, among other treatment modalities, rely on heating tissue to thermal coagulation to treat disease, and are discussed in more detail in the following sections.

1.2 Thermal Therapy

Thermal therapy refers to the application of heat to treat disease. Over a century ago, thermal therapy was used to treat advanced cancers by inducing fever in patients. Today, modern advances in heating sources, treatment delivery techniques and temperature monitoring technology have given rise to an array of sophisticated treatment approaches to treat localized disease effectively and safely, including cancer of the prostate.

1.2.1 Tissue Destruction with Heat

Similar to radiation therapy, where ionizing radiation is used to deposit energy to kill cells, thermal therapy uses a source of energy to raise the temperature of targeted tissue inducing
cellular necrosis. The mechanisms through which tissue destruction occurs with heat depend on the level of temperature increase, ultimately categorizing thermal therapies into two broad regimes of hyperthermia (low-temperature thermal therapy) and thermal coagulation (high-temperature thermal therapy).

In hyperthermia, tissues are heated moderately to temperatures of 41 to 46°C for hours or several minutes to achieve a therapeutic response through cell death. At these temperatures, changes to the cellular environment, such as a decrease in pH, enhance protein denaturation and inhibit repair of thermal damage [Bicher et al 1980]. In this regime, the temperature and duration of heating are critical variables in the induction of cellular necrosis; for example, raising tissue to 46°C for twenty minutes produces the same therapeutic effect of 43.5°C for almost two hours [Borrelli et al 1990]. Although hyperthermia alone has been shown to be inadequate to obtain a sustained clinical response in the treatment of tumours [Dewhirst et al 1982], its most effective application has been in conjunction with radiation or chemotherapy because the combination of modalities has a synergistic effect [Stauffer and Goldberg 2004]. Specifically, hyperthermia markedly sensitizes hypoxic cells to the cytotoxic effects of radiation and chemotherapy [Kim et al 1975, Dewey et al 1977, Hahn 1979].

Thermal coagulation, or high-temperature thermal therapy, raises target tissues to temperatures between 50°C and 100°C, quickly inducing irreversible structural and chemical changes within the intra- and extracellular environment of cells inducing cellular coagulation and tissue necrosis [Thomsen 1991]. At these temperatures, the time of exposure and control of temperature are much less critical variables because protein denaturation and cell kill occur indiscriminately within seconds [Borrelli et al 1990]. During high-temperature thermal therapy, it is important to ensure that tissues do not exceed 100°C to avoid boiling (water vaporization) and carbonization, both undesirable effects which could interfere with the mechanism of energy delivery.
1.2.2 Thermal Dosimetry

As discussed in the previous section, cell kill through heat is a function of both temperature and time. The thermal dose model developed by Sapareto and Dewey [1984] relates any heating profile to equivalent minutes of heating at 43°C (EM43), an arbitrary reference temperature, according to the relationship:

\[ t_{43} = \int_{t=0}^{t=\text{final}} R^{43-T(t)} \, dt , \]

where \( t_{43} \) is the thermal dose in equivalent time at 43°C (EM43), \( t \) is the time (min), \( T(t) \) is the temperature (°C), and \( R \) is a constant equal to 0.25 and 0.50 for temperatures below and above 43°C, respectively. While different tissue types have different thermal tolerances [Li et al 1989], it is widely accepted that a thermal dose of 240 EM43 is sufficient to cause complete cell death (0.01% cell survival) in most tissue types [Borrelli 1990, Diederich 2005]. It is important to note, however, that some partial thermal damage can occur at thermal doses lower than this threshold.

The thermal therapy technology used in this thesis achieves tissue destruction through thermal coagulation at temperatures greater than 50°C, thus inducing the intended therapeutic effect in a few seconds. At these temperatures, exposure times similar to the temporal resolution of MRI-derived temperature measurements (~5 s) are sufficient for tissue coagulation; therefore, tissues raised to a critical threshold temperature, \( T_c \) (°C), are assumed to be completely killed. In this context, regions of thermal coagulation are defined as \( T_c \) isocontours or isosurfaces, a method shown to represent accurately the spatial extent of tissue damage, as reliably as the thermal dose model described above [Yung et al 2010]. For the technology described in this thesis where tissues are heated to high temperatures (> 50°C) for about 30 s, a critical threshold temperature of 55°C and 52°C is used when discussing acute and late thermal coagulation in vivo, respectively [Puccini et al 2003, Chopra et al 2009].
this is not a definitive threshold in all tissues for all therapies, it is representative, in this context, of thermal coagulation in the prostate.

Conceptually, there is also a region of tissue where some thermal damage has occurred; this is termed the transition zone and it is located between the region of thermal coagulation and the region of tissue that is completely undamaged (where no evidence of thermal damage is observed). In-vivo histological analysis specific to the therapy described in this thesis reveals that the transition zone extends about 3 mm from the region of thermal coagulation when acute effects are observed (approximately the distance from the 55°C to 52°C isotherms), whereas the transition zone is nearly non-existent when late effects are observed [Boyes et al 2007, Chopra et al 2009]. High-temperature focused ultrasound devices (discussed in section 1.3.4) localize energy deposition in a small volume, creating elementary regions of thermal coagulation with very sharp thermal gradients and precisely defined margins to normal tissue, with transition zones on the order 100 μm [Susani et al 1993].

Many terms such as thermal lesion, region of thermal ablation and region of thermal coagulation are used arbitrarily and interchangeably in the literature to describe volumes of complete cell death. For simplicity, region of thermal coagulation will be used throughout this thesis, in accordance with standardized nomenclature for image-guided tumour ablation [Goldberg et al 2005].

### 1.2.3 Heating Sources

A variety of energy sources is used for thermal therapy in clinical practice including ultrasound [Madersbacher et al 1994, Gelet et al 1999], microwave [Harada et al 1985, Sherar et al 2001], laser [Carpentier et al 2008, Lindner et al 2009, Stafford et al 2010] and radio-frequency (RF) [Gazelle et al 2000]. Due to the lack of spatial control over the energy deposition, microwave, laser and RF heating sources are limited to producing spherical or ellipsoidal-shaped volumes of
coagulation using a single applicator. The conformal shaping of the region of coagulation is thus achieved by inserting multiple devices at precise locations throughout the target. The primary shortcoming of these thermal therapy modalities for the management of prostate cancer, therefore, is that it is difficult to heat the entire prostate to coagulation without the insertion of several transrectal and/or transperineal devices increasing the invasiveness of the procedure, or without damaging the important surrounding anatomy. These therapies, however, have shown to be effective in the treatment of simple-shaped targets and tumours which are not adjacent to critical structures, such as in the treatment of BPH [Mattiasson et al 2007] or focal prostate cancer [Lindner et al 2009, Raz et al 2010]. For applications in interstitial focal therapy, the precise insertion and placement of the devices under image-guidance is important to ensure that the region of thermal coagulation overlaps completely with the targeted volume of tissue.

Ultrasound, on the other hand, offers inherent advantages which can provide superior control over the spatial deposition of energy in tissue [Diederich and Hynynen 1999]. First, the depth of penetration of ultrasound in tissue can be varied from millimeters to several centimeters depending on the frequency of transmission, enabling extracorporeal, intracavitary and interstitial energy delivery. Furthermore, the full spatial extent of targeted tissues is treated mainly by active heating rather than by relying on passive heat diffusion, thus enhancing the potential for control and reducing treatment times. Second, ultrasound transducers can be fabricated and shaped to produce custom directional ultrasound fields further improving the controllability of the spatial power distribution in tissue. As a result, ultrasound heating applicators have the capability to deposit energy in well-defined volumes, providing a high degree of control over the spatial pattern of thermal damage.
1.3 Ultrasound Therapy

1.3.1 Fundamental Concepts

Ultrasound waves are mechanical vibrations which can travel in solid, liquid or gaseous media, similar to audible sound waves, however, with frequencies above the range of human hearing. As ultrasonic waves propagate in tissue, they are subject to energy loss through mechanisms of absorption and scattering [Cobbold 2006]. Ultrasound absorption in tissue is the process by which acoustic energy is converted into another form of energy, such as heat or light, the phenomenon which forms the basis of ultrasound thermal therapy. Ultrasound scattering is the random spatial redirection of acoustic energy due to variations in density and compressibility of tissue (or the medium where the ultrasound is propagating). Reflection and refraction of ultrasound is often considered a special case of scattering, where the acoustic energy is redirected in an organized manner. Ultrasound attenuation accounts for both absorption and scattering; after a plane wave of incident time-averaged intensity, $I(0)$ (W), propagates a distance, $x$ (m), through a homogeneous medium of constant ultrasound attenuation, its intensity will be:

$$I(x) = I(0)e^{-2(\alpha_{\text{att}} + \alpha_{\text{abs}})x} = I(0)e^{-2\alpha x},$$

where $\alpha$, $\alpha_{\text{att}}$ and $\alpha_{\text{scatt}}$ are the ultrasound amplitude attenuation, absorption and scattering coefficients, respectively, in nepers per meter (Np/m), and $\alpha = \alpha_{\text{att}} + \alpha_{\text{scatt}}$. It is often convenient to express these quantities in decibels per meter (dB/m), where $\alpha$ (dB) = 8.686 $\alpha$ (Np).

Ultrasound attenuation increases with frequency, and in most tissues follows a relationship:

$$\alpha = \alpha_0 f^n,$$

where $\alpha_0$ is the attenuation at 1 MHz, $f$ is the ultrasound frequency (MHz), and $n$ is the power-law dependence factor, approximately 1 for most biological tissues ($n = 2$ for water) [Cobbold 2006].
1.3.2 History of Therapeutic Ultrasound

Robert Wood (1868-1955) is considered to be the first to report investigations on the effects of high-power ultrasound on biological media. He was inspired after observing the pioneering work of Paul Langevin on the physical effects of high powered ultrasound where he used quartz crystal plates excited at their natural mechanical frequency to create, among other effects, micro-bubbles in water. Wood collaborated with Loomis, a wealthy lawyer, scientist and Wall Street tycoon, who provided an elaborate laboratory in an old mansion for their use in Tuxedo Park, New York. By transmitting ultrasound vibrations to several objects suspended in an oil bath above a quartz crystal, Wood and Loomis demonstrated a plethora of spectacular effects such as the fountain effect, acoustic radiation pressure, heating of liquids and solids, and a variety of biological effects on red blood cells, fish, frogs and mice. Together, Wood and Loomis published in 1927, “The Physical and Biological Effects of High Frequency Sound Waves of Great Intensity” in volume 4 of the *Philosophical Magazine*, a seminal paper and a landmark in ultrasonics with “The Tuxedo Park Experiments” providing the basis of modern medical ultrasound therapeutics [Wood and Loomis 1927].

In the 1940’s, Lynn and his colleagues were the first to focus non-invasively ultrasound waves in tissue, greatly increasing the ultrasound intensity within the sample relative to its surface, and study the ensuing biological effects. Using a grinded, curved, concave quartz crystal transducer, Lynn *et al* [1942, 1944] exposed paraffin, ex-vivo liver and in-vivo central nervous system (CNS) tissue from cats and dogs to focused ultrasound at various intensities, with the goal of producing localized ablation within the sample without affecting the intervening medium. While they observed melting of the paraffin at the ultrasound focus (melting point of 58°C) [Lynn *et al* 1942], they attributed the damage observed in the in-vivo CNS tissue to the mechanical tearing of the tissue architecture [Lynn and Putnam 1944].
The first medical application of focused ultrasound was performed in the 1950’s by the Fry brothers, Francis and William, whose early work concentrated on the extra-corporeal treatment of various neurological disorders, although removing a portion of the skull to form an acoustic window. Using a combination of quartz crystal transducers and acoustic lenses, the Fry brothers developed a novel four-beam focusing irradiator to create focal regions of ablation deep within the brain without injuring the intervening neural tissue. They first studied the reversible and irreversible effects of focused ultrasound on the CNS of cats [Fry et al 1954, 1955] and subsequently in humans, with initial applications aiming to treat Parkinson’s disease [Fry and Fry 1960]. Despite having developed elaborate position systems to deliver accurately focused ultrasound to specific regions in the brain, the Fry brother’s work was limited by the lack of image guidance to plan and deliver their treatments.

In the 1960’s, Lele made a profound impact on ultrasound therapeutics by demonstrating that the primary mechanism of tissue destruction was indeed thermal [Lele 1967]. He showed that the temperature of the tissue at the time of ultrasound irradiation was a critical variable effecting the dosage-lesion relationship, in other words that the lesion size was directly related to temperature.

The first therapeutic ultrasound device to receive approval from the United States Food and Drug Administration (FDA) was the Sonocare CST-100, developed in the 1980’s for the treatment of glaucoma, based on the work of Lizzi and Coleman [Coleman et al 1985]. Even though several CST-100 units have been sold and hundreds of patients treated, its clinical use has been superseded by laser techniques.

During the late 1980’s and 1990’s, Chapelon and his colleagues at the French National Institute of Medical Research (INSERM) in Lyon studied the effects of high-intensity focused ultrasound (HIFU) on malignant tissue with the purpose of developing a system for cancer therapy [Chapelon et al 1992]. Together with Gelet and his colleagues at Edouard Herriot
Hospital and in collaboration with EDAP, they developed the Ablatherm® device and treated the first prostate cancer patients using HIFU by focusing the ultrasound energy through the rectum into the prostate [Gelet et al 1996].

Today, thousands of patients have been treated successfully in Asia [Uchida et al 2006], Europe [Blana et al 2008, Poissonier et al 2007, Crouzet et al 2010] and North America with EDAP’s Ablatherm® and Focus Surgery’s Sonablate® HIFU systems which were approved by Health Canada in April 2003 and June 2005 respectively [Canadian Agency for Drugs and Technology in Health 2006]. In fact, transrectal prostate ultrasound therapy with the Ablatherm HIFU system is available privately in Toronto at a cost of about $20,000 per treatment [Maple Leaf HIFU 2006].

The Ablatherm and Sonablate devices use a combination of imaging and geometrically-focused therapeutic transducers to guide the delivery and generate focal regions of coagulation in the prostate. To treat the entire prostate volume, mechanical movement of the device is required. InSightec’s ExAblate®, on the other hand, takes advantage of a phased-array transducer design (with about a thousand elements) to steer the acoustic focal spot electronically; this reduces the amount of mechanical movement required to treat the prostate by adjusting the phase of the drive signal of each transducer element. The ExAblate also takes advantage of Magnetic Resonance Imaging (MRI) to guide the treatment delivery, as discussed in more detail in section 1.4.

1.3.3 Generating Ultrasound for Therapy

Modern advances in electronics, material science and imaging technology have facilitated the ability to generate high-power, high-frequency ultrasound at precise locations in tissue all the while reducing the cost of developing such systems, sparking a renewed interest in ultrasound therapy applications over the last few decades.
Quartz crystals were used by Langevin, Wood and Loomis, Lynn and the Fry brothers to generate ultrasound due to their piezoelectric properties. A material exhibits the direct piezoelectric effect when a mechanical strain produces a proportional electric polarization. Applying a force on a piezoelectric material will therefore generate a potential difference between two conducting surfaces in contact with that material, the polarity changing signs when the force is applied in the opposite direction. The inverse piezoelectric effect is where an applied electric field produces a change in material dimension. Piezoelectric materials thus convert mechanical energy into a polar charge and vice versa.

Today, ultrasound transducers are usually piezoceramic in nature (instead of crystals) because they can be easily fabricated, cut and diced into a variety of shapes and arrays, and the direction of their polarity can be controlled. The most widespread piezoceramics are composed of lead zirconate and lead titanate solid solutions, usually referred as PZT. Piezoceramic transducers convert electrical energy into mechanical energy; by applying a high frequency sinusoidal voltage across two conductors bonded to the piezoceramic, the transducer will vibrate (expand and contract) at the same frequency and generate longitudinal pressure (acoustic) waves. The high frequency electrical signals are produced using signal generators and amplifiers, with electrical matching circuits to transfer maximum power to the piezoceramic transducer.

Several interstitial, intracavitary and extracorporeal devices have been designed to deliver focused or unfocused ultrasound energy to a number of anatomical sites in the body, including the uterus (uterine fibroids) [Fennessy and Tempany 2005], prostate [Diederich and Hynynen 1990, Chopra et al 2005, Nau et al 2005], brain [Hynynen et al 2004, McDannold et al 2010], bone [Li et al 2010], colon [Lafon et al 2000], esophagus [Melodelima et al 2006], breast [Hynynen et al 2001, Furusawa et al 2006], liver [Seket et al 2007, Quesson 2010, N’Djin et al 2010] and heart [Yin et al 2006, Pichardo and Hynynen 2009].
1.3.4 High-Intensity Focused Ultrasound for Prostate Therapy

High-intensity focused ultrasound (HIFU) therapy uses externally located transducers to produce a focused beam of sound within the body. At the focal point, a localized volume of tissue often about the size of a small grain of rice ($\leq 0.1$ cm$^3$) can be coagulated in seconds while sparing intervening tissues from thermal damage. A precise volume of tissue can be treated by scanning the focal spot discretely throughout the target, either by mechanical movement of the transducer or by electronic beam-steering using phased-array transducers. The advantages of this delivery approach are the completely non-invasive nature of the therapy, and the high spatial resolution of the treatment delivery due to the small focal coagulation volume. The acoustic properties of bone and gas, however, are drastically different from those of soft tissue, thus impeding ultrasound propagation due to significant reflection, attenuation and defocusing of the ultrasound beam. These effects can be accounted for in special situations such as the skull [Hynynen et al 2004], but generally make treatment of tissue in the vicinity of bone and gas extremely challenging. The juxtaposition of the prostate gland relative to the pelvic bone and rectum make extracorporeal ultrasound therapy impractical for this organ.

Minimally-invasive, intracavitary or interstitial ultrasound heating applicators have been implemented for the treatment of localized prostate cancer. Transrectal HIFU is the most common approach, employing a focused transducer located in the rectum to generate a region of thermal coagulation within the prostate gland. The main shortcoming of transrectal HIFU, however, lies in the fact that the ultrasound energy passes through the rectum, the very organ that must be spared from thermal damage. To avoid undesirable thermal damage in this tissue, long pauses are used between ultrasound sonications to allow the absorbed energy to dissipate and the rectal tissue to cool, thereby limiting the accumulated thermal dose [Poissonier et al 2007]. This results in long treatment times, on average more than 160 minutes to coagulate a typical prostate volume of 36 cc [Blana et al 2008]. Moreover, current clinical systems employ
rather crude image-guidance, using ultrasound imaging to delineate the prostate boundary and visualize the formation of the focal regions of coagulation. Due to the limited information provided by ultrasound-guidance, it can be difficult to ensure adequate overlap of adjacent focal regions of coagulation across the entire target volume, and any surviving tissue within the target volume increases the chance of cancer recurrence [Poissonier et al 2007]. MRI-guided transrectal HIFU systems, such as InSightec’s ExAblate, are under development in an attempt to provide better anatomical images of the prostate for treatment planning (especially useful near the prostate apex), and quantitative temperature measurements within the prostate for safer and more effective treatment delivery. While the ultrasound-guided Ablatherm and Sonablate devices have been used to treat patients for several years (as discussed in section 1.3.2), the MRI-guided ExAblate system is in early clinical use, having treated seven patients as of August 2010 [InSightec 2010].

1.3.5 Interstitial High-Intensity Contact Ultrasound for Prostate Therapy

Interstitial devices can access prostate cancer directly, bringing the energy source as close as possible to the target tissue and eliminating the need for ultrasound to traverse the rectum or other sensitive structures. Interstitial and transurethral device designs are very similar (they are both catheter based) and thus the various device designs are discussed in the following section. Interstitial devices are usually inserted through the perineum into the prostate increasing the invasiveness of the procedure relative to transrectal or transurethral minimally-invasive devices. Similarly to interstitial photothermal therapy [Raz et al 2010, Stafford et al 2010], interstitial ultrasound devices are good candidates for the focal treatment of prostate cancer, given accurate device placement within the prostate.
1.3.6 Transurethral High-Intensity Ultrasound Prostate Therapy

In transurethral ultrasound therapy, heating applicators are inserted through the urethra, making contact with and delivering ultrasound energy directly into the prostate gland. In this configuration, a larger volume of tissue can be exposed in a short amount of time, ultimately resulting in significantly reduced treatment times (about 30 min for prostate volumes that would take over 160 min with transrectal HIFU). A linear array of transducer elements emits directional (but unfocused) high-intensity ultrasound energy directly into the adjacent prostate, quickly raising tissue temperatures beyond 50°C to thermal coagulation. Dynamic control over the intensity of the ultrasound beams and/or rotation of the transurethral device can shape the pattern of thermal coagulation to the prostate gland, thereby reducing possible damage to important surrounding anatomy such as the rectum, urinary sphincters, neurovascular bundles and pelvic bone [Burtnyk et al 2010a]. Furthermore, transurethral devices are particularly well-suited for ultrasound prostate therapy because they create continuous patterns of thermal damage and meet all the criteria set out by an international task force on focal treatments of prostate cancer [Eggener et al 2007].

A number of transducer designs have been developed for catheter based (interstitial or transurethral) prostate therapy including stationary multi-sectored cylindrical transducers [Kinsey et al 2006], stationary or rotating sectored cylindrical transducers [Hazle et al 2002, Ross et al 2004, Nau et al 2005], rotating curvelinear transducers [Ross et al 2005], and rotating rectangular transducers [Chopra et al 2001, Ross et al 2004, Lafon et al 2004]. A description of these devices is also provided by Diederich et al [2004b]. In general, the more divergent the ultrasound beam, the greater the volume of heated tissue, reducing treatment times but also reducing spatial control over the ultrasound energy deposition. The stationary multi-sectored cylindrical transducers emit ultrasound in all directions simultaneously, potentially offering the shortest treatment times yet the least spatial control. Sectored cylindrical, rectangular and
curvelinear transducers all produce directional ultrasound beams which are, respectively, divergent, approximately collimated and slightly focused. These devices must be rotated in order to heat an entire targeted volume of tissue.

Our group has developed a transurethral ultrasound prostate therapy system that uses rotating planar rectangular transducers to generate conformal thermal patterns in tissue. The system has been designed to provide a high degree of control over the deposition of ultrasound energy in all spatial dimensions. Multiple transducer elements are distributed along the transurethral device, each producing independent, directional, planar ultrasound waves that in turn create collimated heating patterns in tissue, as in Figure 2. The depth of coagulation in the direction of heating can be adjusted at each element by modulating the ultrasound frequency and/or power. Angular control of the energy deposition is achieved by regulating the device rate of rotation. Finally, heating in the direction along the device applicator is controlled and limited by the number and size distribution of the independent ultrasound transducer elements. A cooling circuit flows water of temperature $T_u$ (°C) through the transurethral device to couple the ultrasound into the tissue and cool the surfaces of the transducers. An endorectal cooling device (ECD) with water of temperature $T_{rect}$ (°C) is also used in conjunction with the heating applicators to help protect the rectum from unwanted thermal damage.
Figure 2: Conceptual diagram of the transurethral prostate ultrasound therapy system. The device is inserted in the urethra allowing the transducer elements to produce independent directional ultrasound beams directly in the prostate gland. The ultrasound power and frequency and device rate of rotation can be adjusted to create a region of thermal coagulation that conforms to the prostate shape. The cooling device helps to protect the rectum from thermal damage. [Chopra et al 2010a]

With this transurethral approach, the transducers produce acoustic waves that are not focused and attenuate with distance; therefore, the highest pressures and temperatures occur near the device and decrease with distance. Consequently, if the temperature at the outer boundary of the target tissue is raised to a critical temperature $T_c = 55^\circ C$, all of the intervening tissues will have been raised to at least $T_c$ and are considered thermally coagulated. An exception to this statement is the region immediately surrounding the applicator which is cooled by the water that flows in the transurethral device. Figure 3 illustrates these concepts showing the temperature profile in the direction of heating.
Figure 3: Example temperature distribution along the transducer heating direction. The maximum temperature of intervening tissue occurs near the transducer surface and decreases with distance due to ultrasound attenuation in tissue. The tissue temperature adjacent to the transducer is lower than 37° due to the cooling effect of the water (20°C) that flows through the device.

1.3.6.1 Effect of Ultrasound Frequency

The ultrasound frequency determines the depth of ultrasound energy penetration in tissue; ultrasound attenuation and absorption increase with frequency and, thus, lower frequency ultrasound travels further in tissue before being absorbed and converted to heat, as illustrated in Figure 4. In transurethral prostate ultrasound therapy, lower frequencies create regions of thermal coagulation that extend further from the applicator without overheating intervening tissue [Chopra et al 2003]. Consequently, lower frequencies appear to be more suitable to treat larger prostate glands. Considering, however, that the ultrasound attenuation coefficients of bone are an order of magnitude greater than those of neighboring soft tissues [Fry and Barger 1978, Worthington et al 2002], lower operational frequencies risk creating thermal damage at the surface of, or adjacent to, the pelvic bone before the peripheral prostate tissue absorbs sufficient energy for coagulation. Higher frequencies, conversely, deposit their energy closer to
the transurethral applicator which avoids actively heating the tissues surrounding the prostate; however, the depth of ultrasound energy penetration of these higher frequencies may be inadequate to treat the full spatial extent of typical prostate glands without overheating the intervening tissue. To avoid damage to the surrounding important anatomical structures, it is desirable to operate at the highest frequency with depth of heating adequate to coagulate the prostate gland of prostate cancer patients.

Figure 4: Effect of ultrasound frequency. Tissue temperature versus distance from the transducer (3.5 mm transurethral device radius), showing the effect of two different frequencies operating at equal power (10 W/cm² acoustic, transducer size of 3.5 x 20.0 mm²). Lower ultrasound frequencies heat tissue further away from the transducer with desirable maximum intervening temperatures. While this effect is advantageous for treating larger prostate glands, lower frequencies risk creating thermal damage to structures beyond the prostate boundary.

1.3.6.2 Effect of Ultrasound Power

The appropriate ultrasound acoustic power is related to the rate of energy deposition in tissue. The acoustic power should strike a balance between short treatment times and the maximum temperature of intervening tissue, as depicted in Figure 5. For example, setting the power too low reduces the rate of heating resulting in treatments that rely on heat conduction to
accumulate energy at the prostate boundary. This makes treatments unnecessarily long and more sensitive to effects such as blood perfusion. Power levels that are too high, however, will overheat the intervening tissue before the temperature at the prostate boundary reaches the threshold for thermal coagulation.

Figure 5: Effect of ultrasound power. Tissue temperature versus distance from the transducer (3.5 mm transurethral device radius), showing the effect of three different powers (acoustic, transducer size of 3.5 x 20.0 mm²), operating at equal frequencies (9.1 MHz). Higher ultrasound powers have the ability to heat nearby tissue quickly; however, the rate of energy deposition can be such that the intervening tissues are overheated resulting in boiling and carbonization. Lower powers result in unnecessarily long treatment times. Note that the thermal distribution beyond the coagulated region is similar for these three power levels.

1.4 Image Guidance

Critical to achieving accurate spatial targeting and delivery of ultrasound energy in the prostate is image guidance. First, the target tissue and the surrounding anatomy need to be imaged and identified for treatment planning, and the therapeutic devices must be positioned such that the ultrasound is delivered to the intended location. Second, the tissue properties of the prostate, such as ultrasound attenuation and blood perfusion, have a direct impact on the extent and
degree of the generated heating pattern [Wiart et al 2007]. These tissue properties are difficult to determine precisely *a priori* [Wang et al 1999, Cheng and Plewes 2002, Huttunen et al 2006, Dragonu et al 2009] and can change during treatment [Damianou et al 1997]; thus, the ability to shape the region of thermal coagulation precisely to a target prostate volume depends on active feedback control for which real-time visualization of the damaged tissue or accurate temperature measurements within the prostate are essential. In fact, in the United States of America, temperature measurements within patients are required by the FDA for the clinical use of any thermal therapy [Rivens et al 2007]. Finally, while not critical to the delivery of the therapy, image guidance plays an important role in assessing treatment outcome by identifying regions of thermal coagulation. Image guidance of ultrasound therapies is usually performed using MRI or ultrasound.

Most transurethral ultrasound prostate systems and the ExAblate transrectal HIFU device use MRI-guidance for treatment planning, monitoring, control and assessment. While the cost and accessibility of MRI currently limit its widespread use, the soft-tissue-contrast images and non-invasive quantitative temperature measurements provided by MRI for planning and control, are unparalleled. On the other hand, ultrasound-guidance, used by most transrectal HIFU systems such as the Ablatherm and Sonablate, is widely accessible and offers treatment monitoring at an unmatched temporal resolution.

### 1.4.1 Magnetic Resonance Imaging Guidance

MRI-guided ultrasound therapy was first developed by Hynynen and his colleagues in the early 1990’s [Hynynen et al 1993, Cline et al 1993, Mulkern et al 1997]. Early clinical work using the ExAblate system in the breast [Hynynen et al 2001] and uterus [Tempany et al 2003], used MRI for treatment planning and assessment as well as to monitor temperature changes within the targeted tissue during treatment. Chopra, Bronskill and their colleagues at Sunnybrook
Health Sciences Centre were the first, in 2009, to use MRI-derived temperature measurements to control automatically the delivery of ultrasound energy using a closed-loop feedback algorithm in eight prostate cancer patients [Chopra et al 2010b]. Soon afterwards, the ExAblate system used MRI-derived temperature to control the delivery of transrectal HIFU in seven patients (as of August 2010) [InSightec 2010].

### 1.4.1.1 Device Placement and Treatment Planning

Prior to therapy, MRI provides high-resolution, soft-tissue-contrast images enabling precise localization and placement of devices, as well as target prostate boundary delineation (Figure 6a). Based on device features (for example the acoustic window of a transurethral device), the location of the ultrasound transducer elements can be determined and the position of the device can be adjusted as required for therapy (for example within the prostatic urethra). Additionally, the soft-tissue-contrast images permit the precise identification and delineation of the prostate and surrounding anatomy, allowing the application of sophisticated treatment planning strategies to enhance treatment delivery on a patient-specific basis. To date, MRI offers the most accurate target tissue definition [Jolesz 2009]. As discussed in more detail in Chapter 5, quantitative MRI can also detect and localize cancer within the prostate [Langer et al 2009], offering diagnostic images which could be incorporated seamlessly in the planning of prostate cancer treatments, without the need for image registration between the diagnostic, soft-tissue contrast and temperature feedback images.

### 1.4.1.2 MRI Thermometry and Temperature Feedback Control

MRI thermometry provides non-invasive, quantitative, spatial and temporal temperature measurements, enabling active feedback control to compensate for inter- and intra-patient tissue variability, biophysical tissue changes during treatment, and to ensure adequate and accurate
heating of the target volume [Hutchinson et al 1998, Chopra et al 2009, Arora et al 2006, Mougenot et al 2004, Vanne and Hynynen 2003]. While there are several ways in which MRI can acquire temperature data [Quesson et al 2000], the method using the proton resonance frequency (PRF) shift of water [Ishihara et al 1995] is the preferred choice for most ultrasound therapy applications because of its excellent linearity over the range of temperatures of interest (37 to 100°C), its near-independence with respect to tissue type [Peters et al 1998] and temperature [Kuroda et al 1998], as well as its good temperature sensitivity (for example, accuracy of ±1°C in-vivo at 1.5 T for 5 s image acquisitions).

Briefly, the water PRF, essentially a temperature-sensitive chemical shift, has a linear dependence on temperature of approximately -0.01 ppm/°C [Hindman 1966]. These small shifts in PRF of water can be measured as phase differences acquired using standard gradient echo (GE) imaging sequences. Before heating, a high-SNR baseline phase image, $\phi_{\text{ref}}$, of known temperature is acquired which is subtracted from the phase images acquired during treatment, $\phi_{\text{treat}}$. The difference in phase between the treatment image and the reference image, $\Delta \phi$, is proportional to the temperature change, $\Delta T$ (°C), according to:

$$\Delta \phi = \phi_{\text{treat}} - \phi_{\text{ref}} = \gamma B_0 \cdot \varepsilon \Delta T \cdot TE,$$

where $\gamma$ is the gyromagnetic ratio of water (hydrogen, 42.58 MHz/T), $B_0$ is the MRI magnetic field strength (T), $\varepsilon$ is the proton resonant frequency shift dependence of water (about -0.01 ppm/°C) and $TE$ is the MRI echo time (s). In a 1.5 T MRI, an increase in temperature of 100°C corresponds roughly to a decrease in resonant frequency of 64 Hz.

MRI thermometry, therefore, enables quantitative temperature data of the tissue being heated to be fed back to a controller which can adjust the device output to compensate for tissue irregularities and dynamic tissue property changes that are difficult to predict and model (Figure 6b). The efficacy of using MR thermometry temperature measurements to guide thermal
therapies has been demonstrated by a number of groups [McDannold et al 2000, Vanne and Hynynen 2003, M ougenot et al 2004, Chopra et al 2009, Fuentes et al 2009].

Also of significant advantage is the use of MRI to confirm the location of the HIFU focal spot before treatment. The temperature sensitivity of MRI thermometry using the PRF shift of water enables the visualization of subthreshold heating induced by low-power sonications [Hynynen et al 1997a]. This ensures that the ultrasound propagates and focuses as expected and avoids unwanted heating and damage outside the target tissue.

While MRI thermometry using the PRF shift of water is an effective method to measure temperature non-invasively during ultrasound therapy, certain limitations should be considered. First, all phase changes relative to the baseline image are assumed to be related to temperature; therefore, tissue motion and spatial changes in susceptibility artifacts caused by device movement can compromise the accuracy of the temperature measurements. Several methods are under development to compensate for tissue motion [Pernot et al 2004, de Senneville et al 2007] and moving susceptibility artifacts [Zhou et al 2010]. Moreover, MRI thermometry using the PRF shift of water is sensitive to magnet phase drift, or baseline drift, caused by the temporal instability of the main magnetic field and gradient-induced heating of the magnet components [El-Sharkawy et al 2006]. Typically, the strength of the main magnetic field decreases very slowly over time due to resistive heating of the magnet structures, resulting in apparent (negative) temperature drift which can be different from vendor-to-vendor and magnet-to-magnet (typical temperature drift of the 1.5 T and 3.0 T GE research MRI’s at Sunnybrook Health Sciences Centre is 0.10 and 0.67°C/min, respectively, and M ougenot et al [2009] report a temperature drift of 0.96°C/min using a 1.5 T Philips MRI). The baseline drift can be accounted for and corrected during the calculation of temperature by monitoring the phase in non-heated regions of the images [El-Sharkawy et al 2006, Grimault et al 2004].
Second, the PRF of adipose tissue changes very little with temperature [De Poorter 1995], thereby compromising the accuracy of temperature measurements within or near boundaries of fatty tissue. This is of particular importance in sites such as the breast and can also be of concern when measuring temperature near or beyond the prostate capsule due to the presence of adipose tissue near its periphery.

Finally, the temperature across the entire baseline image must be known in order to calculate the absolute temperature due to some measured temperature change. Typically, baseline phase images are acquired before the application of heat and the baseline temperature can often be assumed constant across the image and equal to, for example, 37°C in vivo.

1.4.1.3 Assessment of Treatment Delivery

MRI is also used to assess the outcome of ultrasound therapy after treatment delivery. Post-treatment, T2-weighted images show the region of coagulation, but it can take several minutes to hours for these changes to appear [Chen et al 1999]. Thermal coagulation can also be visualized using T1-weighted sequences [Graham et al 1999], yielding images with clear demarcations of perfused versus non-perfused tissue when combined with a contrast agent [Hynynen et al 1994, McDannold et al 1998]. Figure 6c shows an example of a contrast enhanced (CE) MRI used to evaluate the extent of thermal damage within the canine prostate by exhibiting signal loss in the coagulated regions due to lack of tissue perfusion.
Figure 6: In-vivo canine MRI-guided transurethral prostate ultrasound therapy. a) Prior to therapy, T2-weighted MRI is used for device positioning and orientation. The prostate and relevant anatomy are imaged for treatment planning. b) MRI thermometry can measure temperature distributions in vivo for active temperature feedback. c) Post-treatment, contrast enhanced (CE) MRI can depict the extent of thermal damage by providing contrast between tissues that are well-perfused and those that are not. This particular experiment delivered two sectored treatments to demonstrate feasibility.

1.4.2 Ultrasound Guidance

Currently, the vast majority of clinical ultrasound therapy procedures are guided using ultrasound, due to the limited number of approved MRI-guided HIFU devices and treatments. While not as accurate as MRI [Lee and Chung 2007], ultrasound can provide anatomical images for 3D target tissue delineation and treatment planning. While also not as promising as MRI [Langer et al 2009], ultrasound has a potential role in the diagnosis and localization of cancer, including that of the prostate [Trabulsi et al 2010].
During treatment, ultrasound offers rather qualitative images of temperature elevation or HIFU focal spot location; therefore, in this context, ultrasound typically monitors treatment delivery as opposed to providing information for automatic feedback control. Conventional ultrasound-guided HIFU procedures rely on an increase in B-mode image brightness (hyperechoic areas) to locate and confirm the formation of an elementary focal region of coagulation. The hyperechogenicity of the focal spot is likely due to the formation of bubbles (cavitation) which backscatter more ultrasound than soft-tissue [Bailey et al 2001, Rabkin et al 2005]. If B-mode hyperecho formation is used for pre-treatment focal spot localization, unwanted and unintentional tissue damage may occur [Rabkin et al 2006]. Additionally, temperature control is often used to avoid cavitation and thus methods that can detect earlier signs of coagulation are desirable.

Ultrasound elastography is being investigated as a means to monitor and possibly control treatment delivery of HIFU procedures. Tissue stress resulting from direct mechanical compression [Stafford et al 1998] or periodic radiation force created using focused ultrasound [Nightingale et al 2001] induce localized tissue displacements which can be measured using cross-correlation techniques. As confirmed by MRI thermometry, a decrease in the amplitude of the tissue displacement is indicative of an increase in tissue stiffness caused by thermal coagulation [Curiel et al 2009a]. Using a threshold displacement value to signal coagulation, this technique showed moderate success to control HIFU treatment delivery [Curiel et al 2009b].

Quantitative temperature measurements using pulse-echo ultrasound have been shown to be feasible, although over a limited range. These methods are usually based on the thermal dependence of the ultrasound echo related to local changes in speed of sound due to temperature and thermal expansion of the propagating medium [Maass-Moreno et al 1996, Simon et al 1998]. Since these two physical phenomena are tissue-type dependent and non-linear outside a
range of 10°C [Liu and Ebbini 2010], pulse-echo ultrasound guidance is limited currently to focal spot localization, treatment monitoring or low-temperature hyperthermia control. Currently, there are no temperature measurement techniques using ultrasound that provide quantitative information over the range of 37°C to 100°C, as required for control of transurethral ultrasound prostate therapy.

Ultrasound offers some advantages over other imaging modalities such as MRI, for guiding thermal therapies. As mentioned previously, ultrasound is relatively inexpensive and accessible. Furthermore, the high temporal resolution offered by ultrasound enables accurate tracking of the temperature dynamics at the HIFU focal spot [Liu and Ebbini 2010]. This is important because the temperature can be underestimated significantly using MRI thermometry when the transients are shorter than the image acquisition time and/or the spatial extent of the peak temperature is within a voxel [Khokhlova et al 2009].

In general, compared to ultrasound, MRI offers superior-quality anatomical images for target definition, tumour identification and treatment planning [Ménard et al 2004, Jolesz 2009], as well as quantitative intra-operative temperature measurements for focal spot localization and closed-loop feedback control. The existing advantages offered by ultrasound-guidance (accessibility and high temporal resolution), combined with recent advances in ultrasound technology, could, however, make it a good modality to guide thermal therapies of the future, or, in the least, become complementary to MRI.

1.5 Research Motivation

Our group has developed a MRI-guided transurethral ultrasound therapy system for the treatment of localized prostate cancer. A rotating applicator housing multiple planar rectangular transducers is used to generate conformal volumes of thermal coagulation shaped to the
geometry of the entire prostate gland. To adjust a heating pattern dynamically to a desired shape, the device rotation rate, ultrasound power and frequency must be tightly controlled. These variables are modulated by a feedback control algorithm which considers the temperature at the target tissue boundary, as measured by MRI thermometry, as well as the depth of heating required. In other words, the control algorithm defines the device parameters in terms of the measured temperatures and spatial anatomical dimensions. It is important to note that the equations governing the rate of rotation and ultrasound power include constants that must be determined for a particular ultrasound frequency using computer simulations. The control algorithm also monitors the maximum temperature inside the target volume to ensure that it does not exceed a threshold such as the boiling point in tissue.

In the case of a device with a single transducer element, adjusting the rate of rotation is sufficient to shape the region of thermal coagulation to a predefined target boundary in a plane perpendicular to the applicator. Since the heating pattern is only controlled in a plane, such treatments are termed 2D. A single-transducer-element control algorithm has been developed with simulations [Chopra et al 2005] and the ability to produce conformal regions of thermal coagulation in vivo in the canine prostate has been demonstrated [Chopra et al 2009]. While the heating pattern was accurately controlled in the axial plane (Figure 7a), conformity in the direction along the device applicator remains a critical, unaddressed issue (Figure 7b).

The feasibility of using temperature feedback for a single transducer element has been shown. The challenges lie in moving to multiple transducers and when considering realistic prostate volumes. The goal of this work was to investigate methods to achieve complete, safe and effective 3D conformal treatments, to heat the entire prostate to thermal coagulation while sparing surrounding anatomy from thermal damage. Specifically, this work aimed to develop and demonstrate a treatment delivery strategy capable of shaping the region of thermal
coagulation produced by multiple transducer elements to predefined target volumes with geometric complexities similar to those of human prostates.

Figure 7: In-vivo canine treatment results of a transurethral prostate ultrasound therapy with a single transducer element and feedback control. Each image is orthogonal to the other as shown by the white dashed lines. a) Axial MRI image (plane of rotation). The heat deposition was controlled in this slice such that the region of thermal coagulation (55°C isocontour) conforms to the predefined target boundary. The target boundary was defined inside the prostate boundary to evaluate the extent of the treatment transition zone by histological examination. b) Coronal MRI image (along device applicator). While the region of thermal coagulation is shaped to the target boundary in the axial image, the coronal image reveals inadequate heat deposition from the single transducer along the dimension of the device applicator.

1.6 Specific Aims

The overall goal of this work was to develop a treatment delivery strategy that uses multiple transurethral ultrasound transducer elements and temperature feedback to shape a region of coagulation to realistic prostate volumes. This was addressed in a series of studies: 1) A simulation study to determine a treatment-delivery, temperature-feedback method and demonstrate the feasibility of performing 3D conformal prostate therapy across a realistic distribution of human prostate volumes [Burtnyk et al 2009]. This study investigated the
physics of ultrasound propagation in tissue to determine how acoustic energy can be delivered with our transurethral device to coagulate realistic prostate volumes accurately and precisely. 2) A simulation study to determine and develop treatment planning strategies that reduce the thermal impact to the important anatomy surrounding the prostate, consequential to 3D conformal ultrasound treatments [Burtnyk et al 2010a]. Heating of the rectum, pelvic bone, neurovascular bundles and urinary sphincters was quantified in realistic 3D anatomical patient models and the damage to these structures, if any, was evaluated using thermal tolerances reported in the literature. 3) An experimental study to demonstrate the feasibility of using MRI temperature feedback to control the spatial heating of 3D conformal ultrasound treatments targeting realistic human prostate volumes in well-characterized tissue-mimicking gel phantoms [Burtnyk et al 2010b]. Finally, the 3D experimental data were used to determine precisely the accuracy with which the numerical simulation calculated or predicted the 3D heating pattern produced in vitro.

The result of this thesis formed the basis of 3D treatment delivery strategies and treatment planning methods used for transurethral ultrasound therapy in patients. Furthermore, the temperature feedback controller developed in this thesis was the first to adjust automatically the position and intensity of multiple ultrasound fields based on temperature measurements in order to shape regions of thermal coagulation to clinically-relevant, large (> 2 cc), realistic 3D target volumes. Finally, this work addresses the feasibility of using this technology for the treatment of localized prostate cancer, and informs the design of prototype patient systems.
2 Temperature Feedback Method and Quantitative Analysis of 3D Treatment Accuracy: Theoretical Simulations

2.1 Introduction

There have been several in-vivo studies demonstrating the technical feasibility of producing large regions of thermal coagulation sufficient for prostate therapy [Kinsey et al 2008, Ross et al 2005, Diederich et al 2004a, Diederich et al 2004b, Hazle et al 2002, Lafon et al 2004, Pauly et al 2006, Chopra et al 2009]. Temperature feedback algorithms for, and quantitative assessment of shaping these regions to human prostate geometries in 3D, however, has not been fully explored. In 2005, Chopra et al introduced a method to generate heating patterns whose 2D central axes conformed accurately to axial planar prostate boundaries using a single large rotating transducer under active temperature feedback control. The situation becomes more complex and the challenges more significant when using a rotating device with multiple transducer elements to shape continuous 3D heating patterns to volumetric prostate geometries for whole-gland treatment. For example, 2D control over the region of thermal coagulation with a single ultrasound transducer was primarily achieved by modulating the device rate of rotation [Chopra et al 2005]. Because all elements of a multiple element transducer rotate at the same rate, the ultrasound power and frequency of each element must be independently controlled to shape 3D heating patterns to complex prostate volumes. Moreover, heat conduction in the prostate from adjacent transducer heating patterns can affect the temperature dynamics, treatment control, and the final spatial heating pattern, ultimately having an impact on treatment accuracy. The goal of this work was to predict with numerical simulations the potential

** This chapter is adapted from Burtnyk et al [2009].
accuracy with which 3D target volumes corresponding to the shapes of human prostate glands could be thermally coagulated with MR-temperature-guided transurethral prostate ultrasound therapy. This study used anatomical models derived from high resolution MR images of prostate cancer patients and detailed numerical simulations of 3D conformal transurethral ultrasound therapy.

### 2.2 Methods

This study used computer simulations, implemented in C++, to evaluate the accuracy with which volumetric regions of thermal coagulation could be shaped to target boundaries using multi-element transurethral ultrasound heating applicators and active temperature feedback. A multi-point feedback control algorithm was developed to modulate device parameters (rotation rate, ultrasound power and frequency) based on a series of temperature measurements along the surface of a target boundary. In order to evaluate the performance of the control algorithm on realistic target boundaries, 3D models were created by segmenting MR images of prostate cancer patients. The robustness of the control algorithm was tested further in a series of simulations where tissue ultrasound attenuation, blood perfusion and temperature measurement accuracy were varied. The simulations calculated the thermal dynamics in real-time (30 min of treatment time was computed in less than 30 min) on a P4, Intel® Core™ 2 Quad CPU, 2.4 GHZ, 8.0 GB RAM computer.

#### 2.2.1 Patient Models

Twenty 3D models were formed by manually segmenting the pelvic anatomy on high-quality MR images of men with clinically significant localized prostate cancer destined for radical prostatectomy (mean [range] age: 60.6 [50-68] years, prostate volume: 32.7 [14-60] cc, n=20).
Approval for this use of the images was obtained from the institutional research ethics board. The multi-slice axial, T2-weighted MR images were acquired using a 1.5 T MRI system (GE Signa Excite, Milwaukee, WI) with an endorectal coil (MedRad, Indianola, PA) combined with a torso phased array surface coil. The images had in-plane voxel size (square) = 0.55 mm, slice thickness = 3 mm (with no interslice gap), TE/TR = 100/6,600 ms, echo train length (ETL) = 16, bandwidth = 41.66 kHz, image size = 256 x 256 pixels, field of view (FOV) = 14 cm, acquisition time = 113 s.

The segmentation was performed by manually contouring the boundaries of the prostate, rectum, bladder, neurovascular bundles and pelvic bone, as well as selecting the location of the urethra in each axial image of the prostate cancer patients (Figure 8a). Because the patient images were acquired without the rigid transurethral device in place, the axial images were translated to align the center of the urethra to a common axis. The prostate boundary was interpolated and sampled at every angular degree from the center of the urethra in axial planes positioned 1 mm apart along the transurethral device, producing an accurate and natural representation of pelvic anatomy such as the example shown in Figure 8b.
Figure 8: Modeling the anatomy of a prostate cancer patient from MR images. (a) The prostate (P), rectum (R), bladder (B), pelvic bone (PB), and neurovascular bundles (N), were manually segmented to create patient-specific anatomical models. The position of the urethra (U) was also recorded to locate the virtual transurethral ultrasound therapy device. (b) The segmented structures were incorporated into numerical simulations to enable quantitative assessment of treatment strategies.

2.2.2 Tissue Models

Thermal coagulation was calculated using a temperature threshold, $T_c = 52^\circ C$, representative of late complete cell kill in vivo [Boyes et al 2007, Puccini et al 2003]. While tissues that reached $52^\circ C$ or more were considered completely coagulated (non-viable), some thermal damage can occur at lower temperatures. Tissues that accumulated a conservative thermal dose less than 30 equivalent minutes at $43^\circ C$ (30 EM43) were considered completely spared from thermal damage [Dewhirst et al 2003].

The control algorithm was tuned and evaluated assuming a constant ultrasound attenuation of 0.5 dB cm$^{-1}$ MHz$^{-1}$ for all tissues. Some studies, however, have observed an increase in attenuation upon thermal coagulation of tissue [Worthington et al 2002, Damianou et
Additional simulations modeling this effect were, therefore, conducted 1) to evaluate the influence of increased attenuation on treatment time, and 2) to assess the robustness of the control algorithm under conditions of variation in tissue properties. For these calculations, ultrasound attenuation was increased linearly and irreversibly from 0.5 to 0.845 dB cm\(^{-1}\) MHz\(^{-1}\) as the temperature rose from 50 to 65°C, consistent with measurements performed on freshly excised canine tissues [Damianou et al 1997]. (Worthington et al (2002) report a 2.7-fold increase in fresh cadaver human prostate ultrasound attenuation over the same temperature range, however, the data by Damianou et al (1997) agree more closely to in-house attenuation measurements and in-vivo ultrasound heating temperatures.) All simulations assumed the ultrasound absorption was equal to the attenuation to maintain conservation of energy.

Blood perfusion was simulated as a constant value which decreased to zero in the regions of thermal coagulation. While the majority of the ultrasound therapy simulations incorporated blood perfusion at a nominal rate of 16 ml min\(^{-1}\) 100g\(^{-1}\), simulations incorporating no blood perfusion as well as increased blood perfusion (32 ml min\(^{-1}\) 100g\(^{-1}\)) were also performed on three patient models. These values span the range of those reported in the literature for in-vivo human prostate tissue [Wiart et al 2007, Buckley et al 2004, Inaba et al 1992].

For all soft tissues, the simulations assumed a density of 1000 kg m\(^{-3}\), specific heat capacity of 3700 J kg\(^{-1}\) °C\(^{-1}\), thermal conductivity of 0.5 W m\(^{-1}\) °C\(^{-1}\), and speed of sound of 1500 m s\(^{-1}\) [Vanne and Hynynen 2003, Boyes et al 2007, Tyreus et al 2002, Duck 1990].

### 2.2.3 Device Configuration

In this study, the size of the virtual individual rectangular transducer elements was set to 4 x 3 mm; a width of 4 mm is typical for transurethral devices and a length of 3 mm provided high treatment spatial resolution along the transurethral applicator while maintaining high acoustic
efficiency (>50%, based on prototype devices). When these small elements are operating alone, however, the attainable depth of heating is limited and as such they are appropriate for transurethral prostate therapy only when they are a constituent of a larger multi-element transducer. Up to seventeen elements were necessary to cover the length of the longest prostate in the 3D models. The spacing between elements was set to 0 mm to model closely prototype devices which have a spacing of 100 µm.

A dual-frequency transducer was used to increase the spatial control over the deposition of energy in tissue [Chopra et al 2003]. Higher frequencies are better suited to treat shallow target radii, especially those near the rectum and neurovascular bundles. Conversely, large target radii are more effectively treated with a lower ultrasound frequency. The resonant frequencies of the transducer were set to 4.7 and 9.7 MHz, consistent with prototype devices [Chopra et al 2003].

To remove thermal losses and to couple the ultrasound into tissue, water flows through the transurethral device. The temperature of the water, Tu, was set to an ambient 20°C. A rectal cooling device [Diederich et al 2004a, Chopra et al 2005, Nau et al 2004] maintained at a temperature of 15°C was modeled in all simulations to help protect the rectal wall. The rectal cooling space was defined as the region 3 mm inferior to the outer rectal wall to account for the thickness of the rectal wall and cooling device following the anatomy of Figure 8a.

2.2.4 Ultrasound and Thermal Calculations

Theoretical simulations of prostate ultrasound therapy were performed using transient acoustic and bio-thermal models implemented in C++. The computational domain was a large 16x16x16 cm$^3$ volume comprised of soft tissue and pelvic bone tissue elements. The free-field complex 3D acoustic pressure distribution, p (Pa), from a single planar rectangular transducer element
was calculated for each frequency (4.7 and 9.7 MHz) using an approximate solution to the Rayleigh-Sommerfeld integral by Ocheltree and Frizzel [1989]:

\[
p = \frac{j\rho c\Delta A}{\lambda} \sum_{n=1}^{N} \frac{u_n}{R} e^{-(\alpha_{\text{att}} + jk)R} \sin\left(\frac{ky\Delta w}{2R}\right) \sin\left(\frac{kx\Delta h}{2R}\right)
\]

where \(\rho\) is the density of tissue (kg m\(^{-3}\)), \(c\) is the speed of sound (m s\(^{-1}\)), \(\Delta A\) is an elemental area in the calculation (m\(^2\)), \(\lambda\) is the wavelength (m), \(u_n\) is the normal surface velocity amplitude of the elemental transducer area (m s\(^{-1}\)), \(R\) is the distance from the field point to the origin of the transducer (m), \(\alpha_{\text{att}}\) is the acoustic amplitude attenuation (Np m\(^{-1}\)), \(k\) is the wave number (m\(^{-1}\)), and \(\Delta h\) and \(\Delta w\) are the dimensions of the elemental area (m). Determining the free-field pressure distribution enabled dynamic and spatially-varying tissue attenuation to be incorporated into the thermal calculations. For each field point in the ultrasound calculation, the total attenuation was obtained by integrating the spatially- and temperature-varying attenuation along the perpendicular distance from the transducer. The acoustic pressure generated by the multi-element transducer was resolved by combining the fields from individual elements operating at independent powers and frequencies. These ultrasound pressure distributions were calculated at a spatial resolution of 0.25 mm (isotropic) to characterize the near field of the transducers and the interactions between neighboring elements.

The ultrasound power deposition, \(Q\) (W m\(^{-3}\)), was determined using the intensity of the acoustic pressure and the ultrasound absorption, \(\alpha_{\text{abs}}\) (Np m\(^{-1}\)), according to [Nyborg 1981]:

\[
Q = \frac{\alpha_{\text{abs}} p^2}{\rho c}
\]

Tissue temperature dynamics due to ultrasound power deposition, heat diffusion and thermal homeostasis from blood perfusion were modeled using an explicit 3D finite-difference time-domain solution to Pennes’ Bioheat Transfer Equation (BHTE) [Pennes 1948]:
\[
\rho c_t \frac{\partial T}{\partial \tau} = Q + \nabla \cdot (k_t \nabla T) - w_b c_b (T - T_b)
\]

where \(c_t\) is the specific heat capacity of tissue (J kg\(^{-1}\) °C\(^{-1}\)), \(T\) is the tissue temperature (°C), \(k_t\) is the thermal conductivity of tissue (W m\(^{-1}\) °C\(^{-1}\)), \(w_b\) is the blood perfusion (kg m\(^{-2}\) s\(^{-1}\)), \(c_b\) is the specific heat capacity of blood and \(T_b\) is the temperature of blood (°C). The tissues in the simulations were considered to be thermally homogeneous, reducing \(\nabla \cdot (k_t \nabla T)\) to \(k_t \nabla^2 T\). The thermal calculations were performed at a temporal and spatial resolution of 1 s and 1 mm (isotropic), respectively, ensuring numerical convergence of the BHTE with sufficient resolution to model the spatial and temporal temperature variations in tissue including sharp thermal gradients at the soft-tissue/ECD interface. Simulation tests with higher spatial or temporal resolution did not produce significantly different results. At \(t = 0\), \(T = T_b = 37\)°C, and the thermal gradient at the computational domain boundary was set to zero.

### 2.2.5 Temperature Feedback

The accuracy of treatment delivery was evaluated independent of temperature measurement accuracy to understand the thermodynamics of transurethral ultrasound therapy. In these “ideal” cases, temperature feedback was sampled at every second, matching the temporal resolution of the thermal calculations, with no measurement noise. In reality, however, the temperature measurements for feedback control are acquired using MR thermometry which has limited spatial and temporal resolution, and noise-limited temperature accuracy. A study by Chopra et al [2006] determined that the ability to create conformal heating patterns with a rotating transurethral device was compromised mainly by the sampling time and noise in the temperature measurements. To study the effects of temperature measurement noise on treatment accuracy, simulations incorporating measurements achievable on a 1.5 T MRI (sample at every 5 s with normally distributed noise of 1°C standard deviation), were performed on all twenty patient
models. To provide a sense of system stability, one patient model was selected to investigate the effects of increasing measurement noise, from 1 to 5°C. All temperature noise simulations were repeated five times to account for the random variations in measurement noise.

### 2.2.6 Control Algorithm

A control algorithm based on multi-plane temperature feedback was developed to produce volumes of thermal coagulation that conform to predefined 3D prostate geometries. Feedback control algorithms have many advantages over open-loop approaches (treatment plans) because they can actively compensate for unpredictable variations in the system, such as dynamic blood perfusion [Lin et al 1990]. In this study, the control algorithm used the temperature at the prostate boundary and spatial anatomical measurements to modulate the applicator rotation rate and the ultrasound power and frequency of each transducer element. The goal of the control algorithm was to raise the temperature of the outer surface of the prostate gland to $T_c$ in one complete rotation of the applicator. A secondary objective of the control algorithm was to prevent tissue temperatures from exceeding an upper limit, $T_h = 90^\circ$C, to avoid undesirable effects such as boiling or tissue carbonization. Although the outer surface of the prostate was chosen as the target boundary in these simulations, a sub-volume within the gland could also be treated using this approach.

As shown in Figure 9, a 3.5 mm radius transurethral applicator housing a multi-element transducer was positioned inside a continuous 3D target boundary (the prostate). Each transducer element ($i = 1...n$) emitted a directional ultrasound beam normal to the transurethral applicator creating directional, collimated heating patterns similar to the temperature profile depicted in Figure 9. Along the direction of heating, the temperature rises quickly from $T_u$, reaching a maximum value, $T_{max,i}$, at about 5-10 mm from the transducer surface, then decreasing and reaching ambient body temperature within a few centimeters. The distance from
each transducer element, $i$, to the 3D target boundary along the direction of heating was defined as the target radius, $r_i$. The control algorithm modulated the transurethral applicator rate of rotation ($\omega$) and the transducer elements’ ultrasound power ($p_i$) and frequency ($f_i$) based on the temperature difference ($\Delta T_{ri}$) between $Tc$ and $Tr_i$, as well as the value of $r_i$. In general, the rotation rate was dictated by the transducer element heating the largest target radius, $r_i$. The control parameters were updated after every temperature measurement and determined according to the following equations:

$$
\omega = \min_{i=1..n} \{ \omega_i \}, \quad \omega_i = \begin{cases} 
\omega_{\text{min}}, & T_{\text{max}} > T_h \\
\omega_{\text{min}} \leq \frac{k_{\omega}(r_i)}{\Delta T_{ri}} \leq \omega_{\text{max}}(r_i), & T_{\text{max}} \leq T_h \text{ and } \Delta T_{ri} > 0 \\
\omega_{\text{max}}(r_i), & T_{\text{max}} \leq T_h \text{ and } \Delta T_{ri} \leq 0 
\end{cases}
$$

$$
p_i = \begin{cases} 
0, & T_{\text{max}} > T_h \text{ or } \Delta T_{ri} \leq 0 \\
p_0 + k_p(r_i) \cdot \Delta T_{ri} \leq p_{\text{max}}, & T_{\text{max}} \leq T_h \text{ and } \Delta T_{ri} > 0 
\end{cases}
$$

$$
f_i = \begin{cases} 
f_{\text{high}}, & r_i < r_f \\
f_{\text{low}}, & r_i \geq r_f 
\end{cases}
$$

where $\omega$ is the device rate of rotation ($^\circ \text{ min}^{-1}$), $k_{\omega}(r_i)$ is the rotational gain constant, $p_i$ is the individual element acoustic power ($W_{\text{acoustic}}$), $k_p(r_i)$ is the power gain constant, $f_i$ is the ultrasound frequency (MHz), $f_{\text{high}}$ and $f_{\text{low}}$ are the high and low ultrasound frequencies of the dual-frequency elements.
Figure 9: Typical temperature profile along the direction of heating of an ultrasound transducer element. The target radius ($r_i$) sampled from the 3D target boundary is used to determine the corresponding element’s ultrasound frequency ($f_i$). The difference ($\Delta T_{ri}$) between the critical temperature ($T_c$) and the target radius temperature ($T_{ri}$) is used to control the element’s power ($p_i$) and the applicator rate of rotation ($\omega$). The maximum temperature ($T_{max,i}$) was monitored to ensure that it did not exceed an upper limit ($Th$) thereby avoiding undesirable effects such as boiling or tissue carbonization.

In order to ensure a contiguous pattern of thermal damage, to minimize treatment times and to reduce heating beyond the region of coagulation, the applicator rate of rotation was continuous and set to the maximum value that still permitted coagulation to the largest target radius, $r_i$. The rate of rotation was inversely proportional to $\Delta T_{ri}$ such that the applicator slowed down when target radius temperatures decreased, allowing greater local energy deposition. The rotational gain constant, $k_{\omega}(r_i)$, decreased with $r_i$ and was determined through a separate series of simple tuning simulations. The maximum rate of rotation was set to 60, 120 or 300° min$^{-1}$, depending on $r_i$, to avoid excessive speeds and to maintain a continuous pattern of thermal damage as $\Delta T_{ri}$ approached zero.

The ultrasound power of each transducer element was proportional to $\Delta T_{ri}$ such that the rate of heating decreased as $T_{ri}$ approached $T_c$. The element requiring the minimum $\omega_i$ was usually operating at $p_{\text{max}}$, while the power of the other elements was set to a value between $p_{\text{min}}$ and
The power gain constant, $k_p(r_i)$, increased with $r_i$, a function determined through a separate series of simple tuning simulations. The value of $p_0$ was set to $p_{max}/10$ to ensure a minimum output power when $Tr_i < Tc$. The maximum time-averaged, continuous-wave, acoustic power, $p_{max}$, was set to 1.2 W (for 4 x 3 mm elements), to avoid $T_{max}$ from attaining $Th$. The power of an element was turned off when either the target boundary or maximum temperature exceeded $Tc$ or $Th$, respectively, allowing tissues to cool.

One exception to the relationships described above is at the beginning of a treatment when the applicator remained stationary and the ultrasound power of all elements was set to $p_{max}$. This enabled the generation of a certain amount of heat before initiating device rotation. The choice between $f_{high}$ and $f_{low}$ was made by comparing $r_i$ to $r_f$, which was set to 13.5 mm. This threshold was determined based on keeping treatment times short, as explained previously by Chopra et al [2005].

The energy deposition per unit volume at a given location is proportional to the acoustic power and time spent heating that location. For the element, $i$, where $\omega_i = \omega$, the energy deposition is proportional to the ratio $p_i/\omega_i$ which is a non-linear (quadratic) function of $\Delta Tr_i$. This enables the controller to adjust the energy output more quickly in response to changes in temperature at the target boundary. Due to the bounds imposed on the ultrasound power and device rate of rotation, as well as the relatively slow rates of temperature change in tissue, the non-linear nature of the controller is not expected to cause larger oscillations in temperatures (compared to a linear model) or lead to system instability.

The control algorithm, based on temperature measurements at the target boundary, performed better than one based on thermal dose in this context of high temperature ultrasound therapy (> 50°C) [Burtnyk et al 2007]. Thermal dose increases extremely rapidly for temperatures above 50°C and approaches a binary model for describing thermal coagulation.
Such very non-linear behavior of the thermal dose model at high temperatures makes it extremely sensitive to temperature measurement noise and update rates, ultimately compromising its utility for controlling coagulation.

2.2.7 Quantitative Analysis of Simulation Results

The simulated treatments were analyzed to determine: 1) the accuracy with which the regions of thermal coagulation conformed to the predefined 3D target boundaries, and 2) the consequential heating of the rectal wall. The region of thermal coagulation included all tissues whose maximum temperature during treatment reached or exceeded $T_c$, and was defined as a 3D boundary equal to the 52°C isosurface. Treatment difference was defined as the distance between the coagulation and target boundaries, in mm. Positive values of treatment difference represented areas where the region of thermal coagulation extended beyond the target boundary (overtreatment), and negative values represented undertreatment. Treatment accuracy was first quantified by calculating the mean and standard deviation of the treatment difference sampled across the entire target boundary. This provided a metric of how well the coagulation boundary matched the target boundary in the context of evaluating the performance of the feedback control algorithm.

The second metric of treatment accuracy was defined as the volume of the treatment difference. The over- and undertreated volumes correspond to the amount of tissue outside the prostate that was coagulated and the amount of prostate tissue that was not coagulated, respectively. These volumes were expressed as a fraction of the prostate volume for comparison across the twenty patient models. While the overtreated volume fraction is an indicator of the extent of thermal damage outside the target boundary, it is the undertreated volume fraction which determines the risk of containing viable cancerous tissue. The total treatment volume difference is the sum of the over- and undertreated volume fractions.
The analysis of the treatment results also examined heating of the rectal wall. This was performed by counting the number of 1 mm³ voxels that constituted part of the rectal wall and absorbed more than 30 EM43. This very conservative threshold in the rectum served as a worst-case scenario for the purposes of this preliminary analysis.

### 2.3 Results and Discussion

#### 2.3.1 Patient Modeling

Analysis of the segmented anatomical data revealed the interesting histogram displayed in Figure 10, showing the normalized distribution of the target radius values for the prostate boundaries of the twenty patient models. The darker bars encompass the target radii sampled across the entire surface of the prostate boundary and the lighter bars represent the subpopulation that lies on the interface of the prostate and rectum. The distribution is normalized such that its total area equals 100%. For example, about 5% of the target radii across the twenty patient models lie between 7 and 8 mm and approximately 4.5% come from areas near the rectum while 0.5% come from other areas of the prostate. The shortest and deepest target radii were 4.9 and 30.4 mm respectively. For each patient, the largest prostate width and height were measured (the horizontal and vertical diameters in the axial inset of Figure 10) as well as the prostate length (along the transurethral applicator) and volume. They were (mean +/- std, [range]): width 47.1 +/- 5.5, [38-57] mm; height 28.9 +/- 5.7, [17-38] mm; length 36.5 +/- 7.4, [27-51] mm; volume 32.7 +/- 14.2, [14-60] cc (n = 20).

The range of target radii impacts the choice of ultrasound frequency used for therapy. From Figure 10, smaller radii are not only found at the base and apex of the prostate gland, but are, in fact, mostly located at the posterior portion of the prostate near the rectum. This means that both short and deep target radii are present in axial planes normal to the transurethral
The accurate and safe coagulation of tissue at depths of 5 to 30 mm with a rotating transducer in an internally-cooled applicator was difficult to achieve with a single frequency. Dual-frequency transducers, however, showed significant improvement in the targeting of tissues over this range of radii while maintaining reasonable treatment times (< 1 hour). It was verified during the tuning of the control algorithm that a 4.7 / 9.7 MHz dual-frequency transducer could provide the necessary flexibility for the treatment of these twenty segmented prostate boundaries.

The treatment of the posterior portion of the prostate (peripheral zone) requires careful attention because it is typically in close proximity to the rectum and is the site of the majority of cancers [Grignon et al 1994]. The ultrasound frequency must be high to achieve accurate targeting of the short target radii in that region while avoiding excessive energy deposition in the rectal wall. A dual-frequency threshold, \( r_f \), of 13.5 mm was selected based on maintaining short treatment times; however, it can be seen in Figure 10, that this threshold is also appropriate for treating radii in the direction of the rectum. The use of dual-frequency ultrasound transducers appears to play a critical role in enabling the thermal coagulation of the posterior and anterior portions of the prostate gland while also minimizing damage to the surrounding anatomy [Wootton et al 2007].

The endorectal coil used to acquire the high quality MR images of the prostate cancer patients was about 5 cm in diameter, occupying a large volume of the pelvic cavity. The coil was designed to be pressed closely against the prostate gland, thereby decreasing the distance between the rectum and prostate and increasing the area of the rectal wall in close proximity to the prostate. Consequently, any heating of the rectum was probably overestimated in this study. Similarly, the endorectal coil may also have affected the distribution of target radius values (Figure 10) by flattening the posterior portion of the prostate.
Figure 10: Normalized distribution of prostate radius values sampled from the images of 20 prostate cancer patients. Prostate radius is the length from the urethra center to the prostate capsule and represents the target radius. The distribution is normalized such that its total area equals 100%. As illustrated in the top-right inset (axial), the dark bars represent samples from the entire prostate boundary while the lighter bars represent samples from the region of the prostate (P) that interfaces with the rectal wall (R).

2.3.2 Transurethral Prostate Ultrasound Therapy Simulations

2.3.2.1 Treatment Accuracy

Treatment simulations performed with constant tissue ultrasound attenuation (0.5 dB cm\(^{-1}\) MHz\(^{-1}\)), variable blood perfusion (16 ml min\(^{-1}\) 100g\(^{-1}\)), “ideal” temperature measurements (no noise, 1 s sampling) and rectal cooling (\(T_{rect} = 15^\circ C\)), produced regions of thermal coagulation that conformed very accurately to the predefined 3D target boundaries of the twenty patient models. In all cases, the standard deviation of the treatment difference was less than 1 mm and the total treatment volume difference was less than 10%, relative to the corresponding prostate volume. Examples are shown in Figure 11 for small, medium and large prostate geometries (17, 37 and 60 cc), with the treatment differences encoded in grayscale on the target boundary surface. The regions of thermal coagulation conformed to within 1 mm of the target boundaries across most of the prostate gland.
Figure 11: Three views of typical treatment results of MRI-guided transurethral ultrasound therapy for (a) small, 17 cc; (b) medium, 37 cc; and (c) large, 60 cc prostates. The orientation is consistent with that of Figure 8. Treatment accuracy was quantified by showing the spatial location of the treatment difference on the target prostate boundary. The region of thermal coagulation was within 1 mm of the target boundary over most of these volumes.

Similar results were obtained for all twenty patient models as summarized in Figure 12a which plots the mean, standard deviation and range of the treatment difference as a function of prostate volume. The mean of the treatment difference was on average 0.17 mm and ranged from -0.1 to 0.3 mm. Even though the minimum was almost always significantly greater in magnitude than the maximum, the mean of the treatment difference remained positive in 95% of cases (19 out of 20). This suggests that the treatment difference was typically small and positive which is desirable when aiming to completely coagulate the entire prostate gland. If desired, the treatment difference could be shifted towards positive or negative values by revised tuning of the control algorithm; therefore, the standard deviation of the treatment difference was used as the quantifiable measure of treatment accuracy. For the twenty patient models, the standard
deviation of the treatment difference ranged from 0.4 to 0.8 mm with an average value of 0.63 mm. The tight standard deviation of the treatment difference (< 1 mm for all target boundaries) is evidence of the strong capability of MRI-guided transurethral ultrasound therapy to create volumes of coagulation that conform very well to a range of different human prostate geometries. While overall treatment accuracy is high, even small positive treatment differences can cause adverse effects, for example at the neurovascular bundles. Chapter 3 presents a study examining the spatial distribution and degree of heating of the surrounding anatomy during treatment to evaluate potential complications associated with transurethral ultrasound therapy.

While Figure 12a shows that overall treatment accuracy is high for various prostate volumes, Figure 12b illustrates that high treatment accuracy is maintained across the entire range of target radius values. The standard deviation of the treatment difference ranged from 0.1 to 0.8 mm with an average value of 0.53 mm, demonstrating that the control algorithm performs well for all target radii.

Figure 12: The treatment difference shown as a function of: (a) target prostate volume, and (b) target radius. The standard deviation of the treatment difference remained less than 1 mm for all patient models, confirming a high degree of treatment accuracy. For all target radius values, the standard deviation of the treatment error remained less than 1 mm from 5 to 30 mm.
The total treatment volume difference ranged from 3% to 8% with an average value of 5.5%, expressed as a fraction of the corresponding prostate volume. The undertreated volume fraction, representing the amount of prostate tissue that might still be viable after completion of the ultrasound therapy, remained smaller than or equal to 4% and reached values below 1%. In order to put these values into perspective, Figure 13 shows the total treatment volume difference (dark bars) and the undertreated volume fraction (light hashed bars) relative to a reference margin that extents 1 mm beyond the 3D target boundary (light solid bars) as a function of prostate volume. The overtreated volume fraction corresponds to the visible portion of the dark bars. For all prostate geometries, the total treatment volume difference was approximately half that of the 1 mm reference margin. The undertreated fraction was more significant for small prostates because in these cases the applicator rotates more quickly, on average, possibly under-sampling the target boundary. Forcing a reduction in rotational speed for these smaller prostates may further improve treatment accuracy. If the undertreated fraction were further reduced through appropriate tuning of the control algorithm, however, the total treatment difference would still remain similar causing an increase in the overtreated volume fraction. Considering that state-of-the-art conformal hypofractionated external beam radiation therapy of the prostate uses 4 mm therapeutic margins (conventional radiation therapy uses a 10 mm margin) [Cheung et al 2005], the advantages of MRI-guidance during transurethral ultrasound treatment are clear.
Figure 13: The treatment difference as a fraction of the prostate volume. The total volumetric treatment difference (dark bars) remained below 8% for all 20 patient models. The undertreated volume fraction (light hashed bars) decreased with prostate volume and ranged from less than 1% to 4%. The overtreated volume fraction is represented as the visible portion of the dark bars. To put these values into perspective, the volume fraction of a reference margin extending 1 mm beyond the prostate boundary is displayed. The total volumetric treatment difference was typically half the volume of the 1 mm reference margin.

2.3.2.2 Heating of the rectum

The thermal impact of transurethral prostate ultrasound therapy on the rectal wall was evaluated by measuring the rectal volume that absorbed a thermal dose of more than 30 EM43, a conservative threshold for partial thermal damage [Dewhirst et al 2003]. Half of the prostate models maintained rectal heating below this threshold, 40% exceeded this threshold in 1 to 5 mm³, and 10% (2 out of 20) in 5 to 20 mm³. In all cases, the volume that exceeded 30 EM43 was limited to the superficial 1 mm layer of the rectal wall.

2.3.2.3 Treatment times

As anticipated, the total treatment time increased with prostate volume. Figure 14 shows that treatment times were typically 30 min and ranged from 15 min for a 15 cc prostate to nearly 60
Simulations which modeled increasing attenuation with temperature were also performed, leading to increased treatment times as shown in Figure 14. The increase in treatment time was greater for larger prostates because energy deposition at deep target radii was reduced and heating from conduction became more important. Treatment times increased by 25% for small prostates (20 cc), by 50% for medium prostates (30 cc) and by 100% for large prostates (>40 cc). These treatment times for transurethral ultrasound therapy remain considerably shorter than those reported for transrectal high intensity focused ultrasound (HIFU).

**Figure 14:** Treatment times for transurethral (TU) ultrasound therapy increase with prostate volume. Treatment times are generally less than 30 min and remain less than 1 hour. When modeling increasing ultrasound attenuation with temperature, a large prostate (59 cc) can be treated in less than 90 min. The mean and range for treatment times reported for transrectal (TR) HIFU are shown for comparison.

### 2.3.3 Temperature Feedback Controller

The feedback control algorithm described in this paper is the first to adjust automatically the rate of rotation and the ultrasound power and frequency of a moving energy deposition field from multiple transducer elements in order to shape volumetric regions of thermal coagulation.
to predefined complex 3D target boundaries. Other studies have used manual adjustments of these parameters [Kinsey et al 2006, Ross et al 2004] or automatic controllers that consider target boundary temperatures of a single ultrasound transducer element [Chopra et al 2005, Salomir et al 2006]. Sophisticated feedback controllers for HIFU or hyperthermia procedures have been described for creating areas of uniform temperature or thermal dose, but the applications have been limited to controlling temperatures at points distributed along a line (1D) or a plane (2D) [Arora et al 2006, Mougenot et al 2004, Vanne and Hynynen 2003].

The control of a transducer with multiple elements is significantly more complex than that of a single element, yet necessary for shaping thermal patterns accurately in 3D. Conformal volumes of coagulation could be produced by translating a single large transducer along the urethra; however, this approach would be highly impractical because treatment times would increase dramatically (by the number of translations) and treatment accuracy would decrease significantly (by having to use a large transducer element).

Figure 15 illustrates the variations in target radius (Figure 15a) along with those which occur for the transurethral applicator rate of rotation (Figure 15b) and the ultrasound power (Figure 15c) and frequency (Figure 15d) of a fifteen-element transducer. At the beginning of the treatment (0 to 2 min), the applicator does not rotate and the power is modulated ON/OFF allowing the generation of an adequate amount of heat. The applicator then rotates slowly while treating the anterior portion of the prostate where some target radii are large (2 to 14 min). During this period, more power is required to coagulate larger target radii. At the posterior of the prostate, when all the target radius values are small (14 to 18 min), the rate of rotation is increased and the power is adjusted accordingly. To reduce treatment times, the rate of rotation is varied such that at least one transducer element is operating at maximum power. The ultrasound frequency is modulated based on target radius values to provide increased accuracy and to decrease treatment times. The ultrasound frequency could also be adjusted in order to
reduce the degree of heating to the surrounding anatomy. It is evident that this level of control made possible using active temperature feedback control could not be achieved manually.

![Diagram](image)

**Figure 15**: Typical variation of rate of rotation and power and frequency of a fifteen-element transducer. Also shown are the current rotational angle and the boundary (target radius) seen by the transducer elements as a function of time. The treatment begins with the device in a stationary position and the power set at maximum to generate a certain amount of heat (0–2 min). Once the device starts to rotate, more power is needed to treat larger boundaries (2–14 min). When the device reaches the posterior region of the prostate where the boundary becomes more shallow, the rate of rotation increases and the power is adjusted accordingly (14–18 min).

### 2.3.4 Effect of Increasing Ultrasound Attenuation with Temperature

Treatment accuracy was evaluated on a representative subset of seven patient models where ultrasound attenuation was increased with temperature. Without adjusting the tuning of the
control algorithm, treatment times increased significantly (Figure 14) thereby increasing the
total energy deposition in the prostate and effectively counteracting the reduction in ultrasound
penetration depth. In all cases, the total treatment volume difference and the standard deviation
of the treatment difference increased; however, a high level of treatment accuracy was
maintained. Figure 16 compares the treatment accuracy, on average, achieved under the
constant and increasing ultrasound attenuation scenarios. The total treatment volume difference
increased on average by 3.4%, from 6.2% to 9.6% (primarily due to an increase in undertreated
fraction), yet remained smaller than the volume of the 1 mm reference margin. The standard
deviation of the treatment difference increased on average by 0.4 mm, from 0.7 to 1.1 mm.

The feedback control algorithm was capable of effectively responding to unforeseen
dynamic changes in ultrasound attenuation to maintain high treatment accuracy with longer
treatment times. In the absence of active feedback control, the system would not be able to
modulate treatment delivery in response to dynamic or unpredictable tissue changes and
treatment accuracy would be severely affected.
Figure 16: The effect of increasing tissue ultrasound attenuation on treatment accuracy when using a control algorithm tuned assuming constant attenuation. The average from seven treatments on representative patient models is shown for constant and increasing ultrasound attenuation. The left side of the figure shows the total treatment volume difference expressed as a percentage of the prostate volume, similarly to Figure 13. The right side of the figure shows the mean, standard deviation, maximum and minimum treatment difference, similarly to Figure 12a. The feedback control algorithm is capable of effectively responding to unforeseen dynamic changes in ultrasound attenuation to maintain high treatment accuracy.

2.3.5 Effect of Blood Perfusion

The rate of blood perfusion in the prostate and surrounding anatomy is highly variable between patients and can influence the depth of heating and temperature dynamics during ultrasound therapy [Wiart et al 2007]. The effect of blood perfusion was investigated in three patient models with small, medium and large prostates (20, 37 and 60 cc). The amount of blood perfusion was varied from 0 to 32 ml min$^{-1}$ 100g$^{-1}$, and affected treatment times and treatment accuracy. Because blood perfusion tends to maintain temperature homeostasis, it has the effect of increasing treatment times on the anterior portion of the prostate, and decreasing treatment times at the posterior where it acts against rectal cooling. For small and medium prostates, therefore, perfusion increased treatment times by less than 10% as can be seen in Figure 17a.
For the larger prostate, however, the anterior portion of the gland is more significant and treatment times increased by more than 40%. The rate of blood perfusion also affected treatment accuracy as shown in Figure 17b. Some amount of blood perfusion is desirable because it damps the temperature response of the tissue and reduces overtreatment. For the small prostate where the applicator rotates more quickly, high levels of blood perfusion can slow the temperature response too much, thereby increasing undertreatment.

Figure 17: The effect of blood perfusion on treatment time and treatment difference shown for small, medium and large prostates. Treatment times increase with perfusion and its effect is more pronounced for larger prostates; from 0 to 32 ml min\(^{-1}\) 100g\(^{-1}\), treatment times increase by <1%, 10% and 40% for the small, medium and large prostates, respectively. Blood perfusion dampens the tissue temperature response and so the total volumetric treatment difference decreases with blood perfusion. A minimum occurred for the small prostate because high levels of perfusion can lead to an increase in undertreated volume fraction.

### 2.3.6 Effect of Temperature Measurement Resolution

Temperature measurement noise and sampling rate can affect treatment accuracy of transurethral prostate ultrasound therapy [Pisani et al 2005, Chopra et al 2006]. To evaluate this effect for a multi-element transducer, treatment simulations were performed with practical 1.5 T MR thermometry temperature measurements with 1°C standard deviation noise, updated every 5 s. In general, treatment accuracy was somewhat reduced as summarized in Table 2 which lists the average, minimum and maximum change from the same results obtained with “ideal”
temperature measurements. On average, the total treatment volume difference increased by 0.40% and the standard deviation of the treatment difference, by 0.10 mm. The volume of the rectal wall that absorbed more than 30 EM43 decreased or remained the same for 95% of the patient models (19 out of 20) across the five repeated simulations. In the single case where rectal wall heating increased, the volume of potentially damaged tissue increased from 1 to 5 mm³.

Table 2: Change in treatment accuracy using practical versus “ideal” temperature measurements for all twenty (nineteen) patient models.

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Time</td>
<td>5 min</td>
<td>20 s</td>
<td>23 min</td>
</tr>
<tr>
<td>Overtreated Volume Fraction</td>
<td>0.25 %</td>
<td>-0.6 %</td>
<td>2.8 % (1.0 %)ᵃ</td>
</tr>
<tr>
<td>Undertreated Volume Fraction</td>
<td>0.17 %</td>
<td>-0.3 %</td>
<td>0.8 %</td>
</tr>
<tr>
<td>Total Treatment Volume Difference</td>
<td>0.40 %</td>
<td>-0.5 %</td>
<td>2.5 % (0.8 %)ᵃ</td>
</tr>
<tr>
<td>Mean Treatment Difference</td>
<td>0.03 mm</td>
<td>-0.1 mm</td>
<td>0.3 mm</td>
</tr>
<tr>
<td>Standard Deviation of Treatment Difference</td>
<td>0.10 mm</td>
<td>-0.1 mm</td>
<td>0.2 mm</td>
</tr>
</tbody>
</table>

ᵃ Values in parentheses refer to the second largest difference in treatment accuracy.

To evaluate system stability, a patient model with relatively complex prostate geometry was used in treatment simulations with increasing levels of temperature measurement noise. Figure 18a shows the qualitative boundary of thermal coagulation with 0, 1 and 5°C standard deviation temperature noise, and the corresponding quantitative treatment difference plotted on the 3D target boundary. The mean, standard deviation and range of the treatment difference is plotted in Figure 18b. There is a gradual increase in treatment difference with temperature noise up to 5°C but the system remains stable.
Figure 18: The effect of temperature measurement noise and sampling rate on the treatment difference for a prostate with complex geometry (32 cc). (a) The qualitative shape of the region of thermal coagulation and the quantitative measure of treatment difference for a patient model with: no noise, 1 s sampling; 1°C standard deviation noise, 5 s sampling; and 5°C noise, 5 s sampling. While the treatment difference becomes noticeable for high levels of measurement noise, treatment accuracy is maintained for practical MR thermometry resolutions (1°C noise, 5 s sampling). (b) The standard deviation and range of the treatment difference increases gradually with temperature measurement noise (up to 5°C), evidence of system stability.

2.4 Conclusions

Regions of thermal coagulation shaped to human prostate geometries with MRI-guided transurethral ultrasound therapy were successfully simulated for a wide range of 3D anatomical models obtained from images of prostate cancer patients. Numerical simulations incorporating multi-element transducer feedback control show that conformal coagulation of the entire prostate gland is possible while avoiding excessive thermal dose to the rectal wall. A high degree of treatment accuracy was achieved over a variety of prostate geometries representative of patients who would be considered for this type of therapy. Heating of the surrounding important anatomy requires further investigations with more suitable anatomical models. Patient-specific treatments incorporating these techniques appear to be feasible.
3 Simulation Study on the Heating of the Surrounding Anatomy during Transurethral Ultrasound Prostate Therapy: a 3D Theoretical Analysis of Patient Safety††

3.1 Introduction

Recent efforts in MRI-guided transurethral ultrasound therapy have focused on device transducer design (multi-sectored cylindrical [Kinsey et al 2006], sectored tubular [Hazle et al 2002, Diederich et al 2004a], curvilinear [Ross et al 2005] and planar [Lafon et al 2004, Chopra et al 2008, Diederich et al 2004b], control algorithm development [Chopra et al 2005, Arora et al 2006, Mougenot et al 2004, Vanne and Hynynen 2003, Salomir et al 2006, Mougenot et al 2009, Burtnyk et al 2009] and in-vivo production of large volumes of thermal coagulation adequate for prostate therapy [Hazle et al 2002, Diederich et al 2004a, Ross et al 2005, Lafon et al 2004, Chopra et al 2009, Diederich et al 2004b, Pauly et al 2006, Kinsey et al 2008]. Prior to clinical use, the treatment accuracy and safety of MRI-guided transurethral ultrasound therapy must be evaluated in a realistic 3D anatomical framework. In Chapter 2, numerical simulations were used to show that MRI-guided transurethral ultrasound therapy is capable of producing highly accurate volumes of thermal coagulation that conform to human prostates within ±1 mm across the vast majority of the gland (14-60 cc, n = 20) [Burtnyk et al 2009]. To assess treatment safety, however, an analysis of the thermal impact of this therapy on the surrounding tissues is required. Wootton et al [2007] used numerical simulations to investigate the thermal impact on pelvic bone during transurethral high intensity ultrasound therapy and showed that excessive heating might occur depending on the transducer design, ultrasound frequency and

†† This chapter is adapted from Burtnyk et al [2010a].
power as well as the dimensions of the prostate and the distance to the bone. This study was limited, however, to 2D ultrasound and thermal calculations and used simplistic patient anatomy derived from geometric shapes.

This work uses 3D anatomical models derived from high resolution MR images of prostate cancer patients and detailed numerical simulations of conformal transurethral ultrasound therapy to quantify and evaluate the thermal impact of such treatments on the surrounding anatomy. The rectum, pelvic bone, neurovascular bundles (NVB) and urinary sphincters were each considered because damage to these structures can create treatment complications [Potosky et al 2004]. Computer simulations are particularly well-suited for this investigation compared to preclinical, in-vivo models. MRI thermometry, based on the PRF-shift of water, is difficult if not impossible to perform in the anatomy surrounding the prostate due to the presence of fatty tissue and the spatial relationship between the various anatomic structures is substantially different between preclinical, in-vivo, prostate models (canine) and humans. This study also determined which parameters strongly influence the heating of the surrounding anatomy and investigated strategies to avoid or reduce thermal damage to these structures. The size of the endorectal cooling device (ECD) can cause spatial anatomical distortions which impact the thermal dose delivered to the surrounding structures; therefore, both large and small ECDs were investigated by creating patient models using images acquired with and without an endorectal MR imaging coil, respectively.

3.2 Methods

In order to consider realistic spatial relationships between the various anatomical structures, complete 3D pelvic models were created by manually segmenting the relevant structures on MR images of prostate cancer patients. A feedback control algorithm adjusted the ultrasound power
and frequency of each element of a linear rectangular transducer array as well as the device rate of rotation, based on temperature and spatial measurements made at the prostate boundary [Burtnyk et al 2009]. Heating of the surrounding anatomy was quantified using the thermal dose delivered to each structure relative to thermal tolerances reported in the literature.

### 3.2.1 Patient Models

Twenty 3D models were formed by manually segmenting the pelvic anatomy on high quality MR images of men with localized prostate cancer destined for radical prostatectomy. Approval for this use of the images was obtained from the institutional research ethics board. The multislice axial, T2-weighted MR images were acquired using a 1.5 T MRI system (GE Signa Excite, Milwaukee, WI). Half of the patient models were created using images acquired with an 8-channel torso phased array surface coil, providing an in-plane voxel size of 0.78 mm and a slice thickness of 3 mm with no interslice gap (mean [range] age: 57.1 [46-64] years, prostate volume: 36.2 [16-60] cc, n = 10). The other half of the patient models was created using images acquired with an endorectal (ER) coil (MedRad, Indianola, PA) combined with a 4-channel torso phased array surface coil providing an in-plane voxel size of 0.55 mm and a slice thickness of 3 mm with no interslice gap (mean [range] age: 60.0 [50-67] years, prostate volume: 33.4 [15-58] cc, n = 10). These two groups approximated patient geometries with a small and large ECD, respectively.

The boundaries of the prostate, rectum and pelvic bone were outlined and the location of the urethra was determined in each image (Figure 19a and Figure 19d). Because the images were acquired without a rigid transurethral device in place, they were translated slightly to align the center of the urethra to a common axis. The pelvic bone was modelled as a 3 mm layer of cortical bone surrounding trabecular bone [Connor and Hynynen 2004, Anderson et al 2005]. Based on measurements summarized in Table 3 and Table 4, the thickness of the rectal wall was
considered to be 6 mm and 3 mm for the patients without and with the MRI ER coil, respectively, corresponding to a small ECD diameter of approximately 1.4 cm and a large ECD diameter of about 4.1 cm. Since the NVB could not be clearly identified in the MR images, their locations were determined according to the description of Lepor et al [1985], a method adopted in other studies examining NVB radiation dose [DiBiase et al 2000]. Specifically, the NVB were considered to lie posterior-laterally, 2 mm away from the prostate boundary. There are two urinary sphincters of interest; the internal or involuntary sphincter comprises the bladder neck at the prostate base, while the external or voluntary sphincter lies in the genitourinary diaphragm (GUD) near the prostate apex. Figure 19b and Figure 19e illustrate the various structures considered in the patient models, while Figure 19c and Figure 19f show a 3D representation of the pelvic models providing a realistic framework for the ultrasound and thermal calculations.

**Table 3: Anatomical measurements of the rectum, patients without ER coil (small ECD)**

<table>
<thead>
<tr>
<th></th>
<th>average ± stdev</th>
<th>90th percentile</th>
<th>10th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal wall thickness - measured</td>
<td>5.5 ± 1.4 mm</td>
<td>7.0 mm</td>
<td>4.0 mm</td>
</tr>
<tr>
<td>Rectum outer diameter</td>
<td>26 ± 3.4 mm</td>
<td>30 mm</td>
<td>23 mm</td>
</tr>
<tr>
<td>% rectum &lt; 5mm from prostate</td>
<td>10.2 ± 2.5 %</td>
<td>12.1%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

**Table 4: Anatomical measurements of the rectum, patients with ER coil (large ECD)**

<table>
<thead>
<tr>
<th></th>
<th>average ± stdev</th>
<th>90th percentile</th>
<th>10th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal wall thickness - measured</td>
<td>2.4 ± 0.5 mm</td>
<td>3.0 mm</td>
<td>1.9 mm</td>
</tr>
<tr>
<td>Rectum outer diameter</td>
<td>47 ± 2.3 mm</td>
<td>50 mm</td>
<td>44 mm</td>
</tr>
<tr>
<td>% rectum &lt; 5mm from prostate</td>
<td>11.8 ± 4.1 %</td>
<td>14.9%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>
3.2.2 Ultrasound and Thermal Calculations

The ultrasound and thermal calculations used in this study were similar to the ones described in Chapter 2, however modified to consider ultrasound interaction with bone. Due to the relatively high thermal conduction of cortical bone, the thermal simulations examining heating of the pelvic bone required a temporal resolution of 0.2 s to ensure numerical convergence of the BHTE.

As summarized by Wootton et al [2007], ultrasound interaction with bone is complex, with the transmission and reflection of longitudinal waves and the generation of highly absorbing shear waves having an angular dependence. For worst-case bone heating, a full transmission model was employed at the soft-tissue/bone interface where all ultrasound energy was transmitted and absorbed into the bone independent of incident angle [Tu et al 1994].

The patient models, composed of soft-tissue and bone (cortical and trabecular), had acoustic and thermal properties summarized in Table 5. These parameters were held constant with temperature, except for blood perfusion which was reduced to zero in regions of thermal coagulation. The ultrasound absorption was equal to the attenuation (no scattering), to preserve conservation of energy.

Selecting appropriate values for the acoustic and thermal properties of cortical bone was challenging because the literature values often do not distinguish between compact and spongy types of bone, and there is inter-subject variability of bone composition. When a range of values was found, the parameters were set to provide increased heating in bone. In particular, the values of thermal conductivity of cortical bone span an order of magnitude; simulations were performed using values of 0.6 W/m°C [Duck 1980] and 2.3 W/m°C [NCRP 1992]. The ultrasound energy and consequential heating are restricted to the 3 mm layer of cortical bone making the simulation results less sensitive to the values used for trabecular bone.
Table 5: Physical parameters used in acoustic calculations and biothermal simulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Soft tissue&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Cortical bone&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>Trabecular bone&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density $\rho$ (kg m$^{-3}$)</td>
<td>1,000</td>
<td>1,700</td>
<td>1,300</td>
</tr>
<tr>
<td>Speed of sound $c$ (m s$^{-1}$)</td>
<td>1,500</td>
<td>2,333</td>
<td>1,500</td>
</tr>
<tr>
<td>Specific heat capacity $c_v$ (J kg$^{-1}$ °C$^{-1}$)</td>
<td>3,700</td>
<td>1,600</td>
<td>1,600</td>
</tr>
<tr>
<td>Thermal conductivity $k$ (W m$^{-1}$ °C$^{-1}$)</td>
<td>0.5</td>
<td>0.6 or 2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Attenuation $\alpha_{att}$ (Np m$^{-1}$ MHz$^{-1}$)</td>
<td>5.8</td>
<td>250</td>
<td>5.8</td>
</tr>
<tr>
<td>Perfusion $w_b$ (ml min$^{-1}$ 100g$^{-1}$)</td>
<td>16 (0 – 32)</td>
<td>0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Duck 1990, <sup>b</sup> Wiart et al 2007, <sup>c</sup> Wootton et al 2007, <sup>d</sup> NCRP 1992

### 3.2.3 Device Configuration

Briefly, the transducer was modeled as a linear array of seventeen, 4 x 3 mm rectangular elements, to cover the length of the longest prostate in the 3D models, identical to the descriptions in Chapter 2. For each patient model, power was delivered only to the transducer elements that were within the prostatic urethra (9 to 17 elements depending on the prostate size).

Due to the frequency dependence of ultrasound attenuation, higher frequencies ($f_{high}$) are better suited to treat tissues at shallow distances from the device as well as to restrict the energy deposited in surrounding tissues such as the rectum, NVB and pelvic bone. Conversely, tissues at large distances from the device are more effectively treated with a lower ultrasound frequency ($f_{low}$). The majority of the simulations were performed with a dual-frequency transducer which resonated at 4.7 and 9.7 MHz, based on prototype devices incorporating a quarter-wavelength thick PZT front layer, as in Chapter 2. Additional simulations examining heating of the rectum and NVB were also performed using a transducer at its fundamental resonance and third harmonic, namely 4.7 and 14.2 MHz.
To remove thermal losses and to couple ultrasound into tissue, water flows through the transurethral device. The space corresponding to a 3.5 mm radius transurethral applicator was held constant at $T_u$ which was set to 20°C for the majority of the simulations, and to 37°C for a subset of simulations examining heating of the urethral sphincters. An endorectal cooling device (ECD) was modeled in all simulations to help protect the rectum. The rectal cooling space was maintained at a constant temperature, $T_{rect}$, and defined as the region 6 mm or 3 mm within the outer rectal wall for the patient models with small or large ECD, respectively, following the anatomy of Figure 19. The effect of the ECD cooling temperature was investigated in simulations with $T_{rect}$ ranging from 2°C to 37°C.

Figure 19: Modeling the pelvic anatomy of prostate cancer patients (a patient without an ER imaging coil (a, b, c); a patient with an ER imaging coil (d, e, f). The prostate (P), rectum (R), pelvic bone (PB) and urethra (U) are manually segmented from a series of axial T2w MR images (a and d). The location of the neurovascular bundles (NVB) is determined based on the prostate shape [Lepor et al 1985]. The segmented structures are used to create 3D patient-specific anatomical models which are incorporated in the computer simulations of transurethral ultrasound prostate therapy. (b) and (e) show a cross-sectional view of the 3D anatomical models, illustrating the dimensions of the cortical (CB) and trabecular (TB) components of the pelvic bone, as well as the rectal wall (RW) and virtual endorectal cooling device (ECD). (c) and (f) show the complete 3D view of the anatomical models.
3.2.4 Control of Temperature

The 3D temperature feedback control algorithm described in Chapter 2 was used to produce volumes of thermal coagulation that conformed to predefined 3D prostate geometries by using temperature and spatial anatomical measurements to modulate the device rotation rate, $\omega$ ($^\circ$ min$^{-1}$), and the ultrasound power, $p_i$ (W), and frequency, $f_i$ (MHz), of each transducer element, $i = 1…n$ [Burtnyk et al 2009]. The goal of the control algorithm was to raise the temperature of the outer surface of the prostate gland to a critical threshold representative of thermal coagulation, $T_c$ ($^\circ$C), in one complete rotation of the applicator. A secondary objective of the control algorithm was to prevent tissue temperatures within the coagulated volume from exceeding an upper limit, $Th = 90^\circ$C, within the prostate to avoid undesirable effects such as boiling and tissue carbonization.

In this study, the ultrasound frequency was controlled according to two schemes: (1) treatment time frequency control (TTFC), and (2) surrounding anatomy frequency control (SAFC). TTFC determined the ultrasound frequency of an element based on the prostate radius for that element as described in the equation above. If the prostate radius was less than 13 mm, $f_{high}$ was used, and vice versa. SAFC incorporated the rules of TTFC, but additionally switched to $f_{high}$ in the angular sectors containing rectum and/or NVB tissues, or when the distance from the prostate to the pelvic bone was less than 10 mm.

The target treatment boundary was set equal to the prostate boundary throughout this study. A subset of simulations examining heating of the NVB used treatment margins, where the target boundary was reduced intentionally by a few mm from the prostate boundary, in 5$^\circ$ sectors around the NVB.
3.2.5 Thermal Analysis and Tissue Thermal Tolerances

Complete cellular necrosis of prostate tissue was based on a critical temperature threshold ($T_c$). The region of thermal coagulation (100% cell kill) included all tissues whose maximum temperature reached or exceeded $T_c$, and was defined as a 3D boundary equal to the 52°C isosurface [Chopra et al 2009, Boyes et al 2007, Puccini et al 2003]. To evaluate treatment accuracy, any treatment difference was defined as the distance between the coagulation and prostate boundaries.

While complete coagulation was defined by a temperature threshold, potential treatment complications can occur at temperatures below $T_c = 52°C$. The thermal dose model developed by Sapareto and Dewey [1984], relates any heating profile to equivalent minutes of heating at $43°C$ (EM43), and increases exponentially with temperature and linearly with time. While most soft-tissues are completely coagulated after 240 EM43 [Borrelli 1990, Diederich 2005] (which corresponds approximately in these treatments to $T_c = 52°C$), the prostate, rectum, NVB, urinary sphincters and pelvic bone have different thermal tolerances as summarized in Table 6. A critical assessment of the thermal dose thresholds summarized in Table 6 is included below; however, the precise temperature-time treatment history is not provided in the references and, if different from the average values reported, it could affect these threshold values.

Thermal damage to the rectum was evaluated following the results of Li et al [1989] on late heat damage in normal swine rectum. They used a transrectal microwave radiator to heat the inner rectal wall to temperatures from 43°C to 48°C for 30 min, and evaluated the ensuing late damage on a histological grading system examining the mucosa, submucosa, muscularis and adventia, with a maximum possible damage score of 36 (100%). The authors stipulated that the possible safety limit for clinical hyperthermia was $44 \pm 0.5°C$ for 30 min because they observed only slight heat damage in this group (21% of maximum possible damage). This corresponds to a thermal dose of 42 to 85 EM43, and was considered in this study as a range of \textit{reversible}
damage, beyond which irreversible damage occurs. These values were most likely conservative because the heat generated by the microwave radiator over the time course of 30 min affected all of the layers of the rectal wall; on the other hand, the use of an ECD in transurethral prostate therapy actively cools the rectum from within the mucosa, thereby creating a sharp thermal gradient within the rectal wall and limiting significant heating to the adventia and/or muscularis layers only. A study by Hurwitz et al [2002] examining heat damage to the rectum of humans following external beam radiation and two transrectal ultrasound hyperthermia treatments, determined that Grade 2 proctitis was common in patients whose rectal wall temperature exceeded 40°C. These results are difficult to interpret in this context because exposure to radiation can affect the thermal tolerance of rectal tissue; however, these results should be considered for patients being treated for salvage therapy of recurrent prostate cancer after radiation failure.

Thermal damage to the NVB was quantified based on the histological studies of Vujaskovic et al [1994] on the effects of intraoperative hyperthermia on the canine sciatic nerve. They observed, at twelve months after treatment, a statistically significant decrease in axon, myelin and small vessel percentages, as well as an increase in endoneurial and epineural connective tissue in the nerves heated to 45°C for 60 min (240 EM43). These histopathologic and histomorphemetric changes were present but less severe in the group treated to 44°C for 60 min (120 EM43), and the nerve fibers appeared normal in the group treated to 43°C for 60 min (60 EM43). While linkage with thermal damage to the NVB leading to sexual-related complications is unclear, for the purposes of this study a patient was considered spared from thermal damage to the NVB when the entire length of the structure remained below 120 EM43. This threshold is likely very conservative because the NVB is cooled by its vasculature, and the observed histopathological changes do not imply complete loss of nerve function. Although the vasculature of the NVB was not modeled in this study, the heat sink from these vessels can
decrease hyperthermia temperatures by about 10°C, reducing significantly the thermal dose delivered to these structures [Khan et al. 2007]. Furthermore, it has been shown that during the use of cautery in radical prostatectomy, the NVB can be heated from 45°C to 110°C leading to thermal doses much greater then 240 EM43 [Mandhani et al. 2008]. To simplify the analysis, only the right NVB (left on the MR images) was considered, because the heating to each structure is relatively symmetrical.

Thermal damage to the urinary sphincters was quantified using studies on rabbit thigh muscle by McDannold et al. [2000]. They concluded that minimal necrosis occurred at exposures of 0.5 to 30 EM43, moderate damage from 60 to 240 EM43, and severe damage beyond 240 EM43. For the purpose of this study, the urinary sphincters were considered reversibly damaged if their tissues remained below 60 EM43, the threshold for moderate damage.

Characterizing thermal injury of the pelvic bone requires careful attention. Shimm et al. [1988] noted patient bone pain during clinical hyperthermia treatments at thermal doses as low as 5 EM43; however, due to the intended use of spinal block anesthesia during transurethral ultrasound prostate therapy, bone pain will be unlikely. Lundskog [1972] first reported the effects of temperature on bone in 1972, showing that cellular necrosis in rabbit bone could be achieved at exposures of 50°C for 30 sec (64 EM43). Eriksson et al. [1982, 1983] performed extensive investigations on the time-temperature exposure properties of bone thermal injury and demonstrated that bone is heated at 47°C for 1 min (16 EM43) showed some minor morphological tissue changes. They also reported more significant bone injury after thermal exposures of 47°C for 5 min (80 EM43) and 50°C for 1 min (128 EM43) leading to re-absorption and replacement with fat cells. They observed irreversible bone injury after heating at 53°C for 1 min (1024 EM43) after which healing occurred from surrounding tissues, three to five weeks later. It was only after raising bone tissue to 60°C (1 sec exposure is 2184 EM43)
that they observed permanent cessation of blood flow and obvious necrosis with no signs of repair over periods of 100 days. For this study, thermal doses from 64 to 1024 EM43 were considered as reversible damage, and irreversible damage occurred at exposures beyond 2184 EM43. These values likely remain conservative in terms of treatment complications because bone temperatures commonly reach 70°C at the bone-cement interface during cement polymerization [Noble 1983, Homsey et al 1972, DiPisa et al 1976] and 90°C during bone drilling [Eriksson et al 1984].

Table 6: Tissue thermal tolerances.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Reversible damage</th>
<th>Irreversible damage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>N/A</td>
<td>≥ 52°C</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Rectum</td>
<td>42 – 85 EM43</td>
<td>≥ 85 EM43</td>
<td>d, e</td>
</tr>
<tr>
<td>Pelvic Bone</td>
<td>80 – 1024 EM43</td>
<td>≥ 2184 EM43</td>
<td>f – m</td>
</tr>
<tr>
<td>NVB</td>
<td>60 – 120 EM43</td>
<td>≥ 120 EM43</td>
<td>n – p</td>
</tr>
<tr>
<td>Urinary Sphincters</td>
<td>30 – 60 EM43</td>
<td>≥ 60 EM43</td>
<td>q</td>
</tr>
</tbody>
</table>


3.3 Results & Discussion

3.3.1 Patient models

The prostate cancer patient anatomical segmentations are discussed first because the spatial relationships between the various structures have a significant impact on the thermal dose delivered to them during treatment. Figure 20, Table 3 and Table 4 describe the spatial
distributions of the prostate and surrounding structures for the patient models with small and large ECD. Figure 20a is an axial depiction of the pelvic anatomy illustrating the various measurements used to characterize the prostate (P), pelvic bone (PB), NVB, rectum (R) and ECD. The anatomical distortions caused by the large ECD are evident.

Figure 20b shows the distribution of prostate radius values (radial distance from the urethra centre to the prostate boundary) normalized to 100%. The large ECD compressed the posterior portion of the prostate (peripheral zone), thereby increasing the proportion of small prostate radii (5-12 mm). Because the treatment difference is typically increased for prostate radii of 5-7 mm [Burtnyk et al 2009], the size of the ECD can affect the treatment accuracy of transurethral ultrasound prostate therapy, notably in the peripheral zone where the majority of cancers are found. The ranges of prostate radius values as well as the peaks of the distributions are relatively similar, however, for patients with small and large ECDs.

The size of the ECD impacted the spatial relationship between the prostate and the pelvic bone significantly, as illustrated in Figure 20c which shows a normalized distribution of the radial distance between these two structures. A larger ECD occupied a larger volume in the patient’s pelvis, shifting the prostate closer to the pubic symphysis (by approximately 10 mm for the patient models in Figure 20c). As the ultrasound power decreases with $e^{-2\alpha_s R}$, where $R$ is the distance from the transducer, more heating of the pelvic bone can be anticipated for patients with a large ECD.

Heating of the NVB was influenced by the cooling effect of the ECD. Figure 20d shows the normalized distribution of the distances between the right NVB and the ECD for the patients with large and small ECD. The shapes of these distributions were relatively similar, but the average distance from NVB to ECD decreased from approximately 18 mm to 11 mm with the large ECD (the rectal wall thickness was partially accountable for this difference). Because
tissues closer to the ECD are more effectively cooled, more heating of the NVB can be expected in patients with a small ECD.

Table 3 and Table 4 summarize rectal dimension measurements for patients with a small and large ECD, respectively. Although the rectal wall thickness and rectum outer diameter measurements differed considerably, the volume fraction of rectum (rectal wall) in close proximity to the prostate (< 5mm) was relatively similar for both groups.

Figure 20: The spatial characteristics of the prostate and surrounding anatomy for patient models with a small and large ECD. (a) Schematic illustrating the different spatial measurements. (b) The distribution of prostate radius values, (c) distance from prostate to pelvic bone, and (d) distance from the NVB to the ECD. The large ECD distorts the shape of the prostate, and decreases the distance between the prostate and the pelvic bone as well as the distance between the NVB and the ECD.
3.3.2 Heating of the Rectum

The thermal dose in rectal tissue is shown in Figure 21 as a function of its distance to the coagulation boundary (52°C isotherm), for all patients with three different values of $T_{rect}$ (referred to as ECD temperature hereafter) and the SAFC regime at 9.7MHz. This type of plot encompassed both the spatial relationship between the prostate and the rectum as well as treatment accuracy. Each sample point in Figure 21 represented 1mm$^3$ of rectal tissue; those on the negative x-axis (negative distances) were heated beyond $T_c = 52°C$, and those on the positive x-axis (positive distances) reached a maximum temperature less than $T_c = 52°C$. The region of reversible damage is shown, with the sample points above this range considered irreversibly damaged. The larger spread in the data for patients with a small ECD (Figure 21a) was due to the larger rectal wall thickness.

![Figure 21: Heating of the rectum: (a) patients with a small ECD, and (b) patients with a large ECD. The figures show a log-plot of the thermal dose absorbed in 1 mm$^3$ of rectal tissue as a function of distance to the boundary of thermal coagulation (52°C isotherm) for three ECD cooling temperatures (body temperature, room temperature and 7°C). The region of reversible thermal damage and 240 EM43 are shown for reference. The points to the left of the dotted line (negative distances) represent rectum voxels whose peak temperatures during therapy were greater than 52°C. With a body temperature ECD, portions of the rectum are heated to the level of irreversible damage. As the ECD temperature decreases, the region of thermal coagulation does not extend into the rectum. There is a greater spread in the data points in (a) due to the larger rectal wall thickness. Each figure contains more than 13,000 data points.](image)
Heating of the rectum decreased with distance from the coagulation boundary as well as with cooler ECD temperature. For an ECD temperature of 37°C, heating of the rectum was largely influenced by the spatial anatomical characteristics of the patients and by treatment accuracy; the patients with a large ECD had increased heating of the rectum due to reduced posterior prostate radii (reduced treatment accuracy) and a slightly greater proportion of rectal tissues in close proximity to the prostate. When the ECD temperature was set to or below room temperature, however, cooling from the ECD became dominant over the spatial anatomical differences. Figure 21 shows that for an ECD temperature of 22°C and 7°C, the volume of irreversibly damaged rectum is similar for patients with small or large ECD (also summarized in Table 7). An ECD temperature of 22°C was sufficient to restrict, in 80% of the patients in each group, the volume of irreversibly damaged rectal tissue to less than 10 mm$^3$ on the outer 1 mm layer of the rectal wall. Heating of the rectum could be further reduced, but not eliminated in all patients, by decreasing the ECD temperature. At an ECD temperature of 7°C, a few small irreversibly damaged volumes remained (3 patients with small ECD: 3, 2 and 1 mm$^3$; 1 patient with large ECD: 4 mm$^3$). These volumes were very small and limited to the superficial layer of the outer rectal wall; thus, they would most likely not have a great impact on patient safety. A 3D view of the worst- and typical-case rectum heating is shown in Figure 22 for the three ECD temperatures. While the region of irreversible damage was extensive across the rectal wall for an ECD temperature of 37°C, the region of heating was spatially limited in the typical-case and worst-case for ECD temperatures of 22°C and 7°C, respectively.

A trade-off existed between using colder ECD temperatures and the resulting treatment accuracy of the posterior prostate (peripheral zone) where the majority of cancers are detected. Using a colder ECD temperature increased the undertreated portion of the posterior prostate, thereby increasing the risk of cancer recurrence. Table 7 lists the volumes of irreversibly damaged rectum and the corresponding volumes of undertreated prostate for the three ECD
temperatures. Reducing the ECD temperature from 37°C to 22°C provided a major improvement in rectal safety for a moderate loss in treatment accuracy. Further reducing the ECD temperature to 7°C provided further minor improvements in rectal safety with a larger penalty in treatment accuracy. The challenge remains, however, to identify prior to therapy, that small fraction of patients (approximately 20%) that would benefit from ECD temperatures colder than 22°C. Reducing the ECD temperature from 37°C to 7°C increased the average treatment time by about 2 min (range was 20 s to 8 min).

Figure 22: Visualizing the thermal impact of transurethral ultrasound prostate therapy on the rectum. For each case, a 3D view of the heating on the outer rectal wall is shown (anterior rectum, portion neighboring the prostate) along with a cross-sectional view showing the maximum extent of heating within the rectal wall. (a) Worst-case heating of the rectum for three ECD cooling temperatures (body temperature, room temperature and 7°C), and (b) Typical case. The dotted lines represent the region of the rectum which neighbors the prostate. The extent of the heating is limited to the superficial 1 mm layer of the rectum only for an ECD below 37°C. While room temperature ECD cooling typically limits the heating of the rectum (b), a small portion of patients requires a colder ECD to provide the same protective effect (a).
The effect of ultrasound frequency on rectal heating was also investigated, using the SAFC regime with a high frequency of 4.7, 9.7 and 14.2 MHz. Because heating of the rectum is largely influenced by the treatment accuracy of the posterior prostate, it was difficult to compare the results of different frequencies for similar ECD temperatures. For patients with a large ECD set to 22°C, a frequency of 4.7 MHz heated, on average, 0.2 mm$^3$ of rectal tissue compared to 7 mm$^3$ with 9.7 MHz; however, the corresponding undertreated prostate volume was, on average, 676 mm$^3$ compared to 68 mm$^3$. To determine the effect of frequency on rectal heating, a common undertreated prostate volume of 70 mm$^3$ was chosen (approximately 2% of the posterior prostate volume neighboring the rectum) and the ECD temperature was varied. For this treatment accuracy benchmark, the irreversibly damaged rectal volume was 173, 15 and 9 mm$^3$ (large ECD), and 390, 1.2 and 17 mm$^3$ (small ECD) for 4.7, 9.7 and 14.2 MHz. Surprisingly, a frequency of 9.7 MHz provided increased rectal safety for patients with a small ECD, probably because the prostate radius values in sectors near the rectum were close to the maximum distance (about 13 mm) that could be coagulated without having intervening tissues exceed $T_h=90^\circ$C at 14.2 MHz. The control algorithm slowed the device rotation to enable heat conduction to reach deep prostate radii, which increased the thermal dose delivered to the rectum. Overall, for the parameters investigated in this study, the best combination of treatment accuracy and reduced rectal heating was achieved by using a small ECD and treating the posterior prostate with 9.7 MHz.
Table 7: Effect of ECD temperature on the heating of the rectum and posterior prostate treatment accuracy. Values shown represent the population average (n=10, each group). An undertreated prostate volume (<52°C) of 70 mm³ represents approximately 2% of the prostate volume neighboring the rectum.

<table>
<thead>
<tr>
<th>ECD temperature</th>
<th>Patients with small ECD</th>
<th>Patients with large ECD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rectum volume &gt; 85 EM43 (mm³)</td>
<td>Prostate volume &lt; 52°C (mm³)</td>
</tr>
<tr>
<td>37°C</td>
<td>136</td>
<td>33</td>
</tr>
<tr>
<td>22°C</td>
<td>8</td>
<td>52</td>
</tr>
<tr>
<td>7°C</td>
<td>0.6</td>
<td>81</td>
</tr>
</tbody>
</table>

3.3.3 Heating of the Pelvic Bone

Heating of the pelvic bone was examined in patients with small and large ECDs, and with a cortical bone thermal conductivity of 2.3 and 0.6 W/m°C (referred to hereafter as high and low $k_{cb}$). Figure 23 shows the thermal dose in the pelvic bone decreasing as a function of its radial distance from the prostate, for each patient group and $k_{cb}$ combination. Each sample point represents 1 mm³ of cortical bone tissue, with the light-colored samples corresponding to simulations using TTFC, and the dark-colored samples using SAFC (operating at 9.7 MHz instead of 4.7 MHz when the pelvic bone is less than 10 mm from the prostate). The 10 mm distance was chosen by examining the low $k_{cb}$ pelvic bone heating of Figure 23c and Figure 23d, where the sample points could potentially become reversibly damaged.

Pelvic bone heating was more important in patients with a large ECD due to the reduced distance between the prostate and pelvic bone (as evident in Figure 20c). Furthermore, a higher value of $k_{cb}$ allowed the heat absorbed in the cortical bone to dissipate to neighboring tissues more quickly, thereby reducing the thermal dose.

For TTFC, patients with a small ECD had, overall, a very small volume of reversible damage and no irreversible damage, for both values of $k_{cb}$ (Figure 23a and Figure 23c). Moreover, by using SAFC in these patients, the pelvic bone could be completely spared from reversible damage.
Figure 23: Heating of the pelvic bone for patients with small and large ECDs, and two values of cortical bone thermal conductivity (low $k_{cb}$ of 0.6 W/m°C and high $k_{cb}$ of 2.3 W/m°C). The figures show a log-plot of the thermal dose absorbed in 1 mm$^3$ of pelvic bone as a function of distance from the prostate. Each plot shows the data for two frequency control strategies: TTFC where the ultrasound frequency is changed solely based on the dimensions of the prostate, and SAFC where the ultrasound frequency is set to 9.7 MHz whenever the pelvic bone is located less than 10 mm away from the prostate boundary. The reversible damage region, irreversible damage threshold and 240 EM43 are shown for reference. A low $k_{cb}$ increases the thermal dose in the pelvic bone. The patients with a large ECD have shorter distances between the pelvic bone and the prostate increasing the thermal dose. In all cases, the heating of the pelvic bone can be limited by using SAFC. Each figure contains over 26,000 data points.

A large ECD pushed the prostate closer to the pelvic bone increasing the potential for bone heating. Patients with a large ECD and a high value of $k_{cb}$ had no irreversible bone damage and the degree and volume of reversible damage could be further reduced with the SAFC approach (Figure 23b). Patients with a large ECD and a low $k_{cb}$ could suffer a small amount of irreversible damage to the pelvic bone when it was located less than 7.5 mm from the
prostate; however, SAFC could eliminate this risk and reduce the volume of *reversible damage* (Figure 23d).

Figure 24 illustrates the impact of ECD size and frequency control approach by showing, for the low $k_{cb}$ value and worst-case patients, the 3D spatial extent of significant pelvic bone heating.

Using SAFC with 9.7 MHz instead of TTFC provided significant improvements in pelvic bone heating and had little impact on overall treatment accuracy.

![Worst-Case Pelvic Bone Heating - Low $k_{cb}$ (0.6 W/m/°C)](figure)

**Figure 24:** Visualizing the thermal impact of transurethral ultrasound prostate therapy on the pelvic bone for the worst-case patients (a and c: with a small ECD; b and d: with a large ECD) assuming a cortical bone thermal conductivity of 0.6 W/m/°C. (a) and (b) show the heating for TTFC, and (c) and (d) show the heating for SAFC with 9.7 MHz. The dotted lines show the region of the pelvic bone which neighbors the prostate. While the patients with a small ECD have limited heating even with the TTFC, the SAFC approach can reduce the thermal dose to within safety limits for all patients.

### 3.3.4 Heating of the NVB

The NVB are at risk of thermal damage during transurethral ultrasound therapy due to their close proximity to the prostate. If the NVB are not localized and accounted for during treatment planning, the treatment delivery cannot perform any adjustments in an attempt to reduce the
delivered thermal dose (TTFC and no treatment margin, i.e.: the entire prostate is targeted). Under these conditions, no patients with a small ECD and 30% of patients with a large ECD had their NVB completely spared from thermal damage (< 120 EM43 along the entire length of the NVB). If the NVB can be localized during treatment planning, however, the target boundary can be reduced intentionally in regions near the NVB (treatment margins). Table 8 summarizes the effects of using SAFC at 9.7 MHz and treatment margins on NVB heating. Using SAFC and 4 mm treatment margins, the proportion of patients whose NVB was spared from thermal damage increased to 90% in patients with a small ECD. The remaining 10% (one patient) did not benefit from increasing the margin even up to 6mm. Due to the increased proximity of the NVB to the rectum in patients with a large ECD, treatment margins of 2 mm were sufficient to spare the NVB from thermal damage in all patient models examined in this study.

![Figure 25: Visualizing the thermal impact of transurethral ultrasound prostate therapy on the NVB for a patient with a small ECD. (a) The thermal dose absorbed along the right NVB with the prostate treatment accuracy achieved using no treatment margins. (b) By defining a 2 mm treatment margin, the thermal dose in the NVB is greatly reduced with only a small section reaching 120 EM43. (c) A 4 mm treatment margin completely spares the NVB from thermal damage, with greater loss in treatment accuracy.](image)

While reducing the target boundary in particular sectors of the prostate decreased the thermal dose delivered to the NVB, this was achieved at the expense of increased prostate undertreatment and, consequently, greater risk of cancer recurrence. The NVB heating and treatment accuracy trade-off is illustrated in Figure 25 for one patient with a small ECD. A 2-
mm margin provided a significant reduction in NVB heating and a modest decrease in treatment accuracy, but larger treatment margins may be required to spare the NVB completely from thermal damage at a greater cost in prostate undertreatment. Figure 25 also illustrates how with MRI-guided transurethral ultrasound prostate therapy, the high degree of spatial control over the volume of thermal coagulation enables the consideration of such safety/accuracy trade-offs. Identifying the location of the NVB and incorporating that information into treatment planning, remains, however, a critical challenge.

The results described above were for SAFC with 9.7 MHz and an ECD temperature of 22°C. When no treatment margin reduction was used, increasing the SAFC high frequency to 14.2 MHz or reducing the ECD temperature to 2°C did not reduce NVB heating to below 120 EM43 in the patients with a small ECD. NVB heating was reduced to below 120 EM43 in one patient (10%) with a large ECD, by increasing the frequency to 14.2 MHz or by decreasing the ECD temperature to 17°C.

Table 8: Percentage of patients whose NVB is spared from thermal damage (< 120 EM43 along the entire NVB).

<table>
<thead>
<tr>
<th>TTFC</th>
<th>SAFC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no margin</td>
</tr>
<tr>
<td>Patients with small ECD</td>
<td>0%</td>
</tr>
<tr>
<td>Patients with large ECD</td>
<td>30%</td>
</tr>
</tbody>
</table>

3.3.5 Heating of the Urinary Sphincters

The internal and external urinary sphincters, near the prostate base and apex respectively, are not located in the direct path of ultrasound power deposition; therefore, the primary heating source of these structures is heat conduction from neighboring prostate tissues as opposed to ultrasound energy absorption. To characterize the heating of the urinary sphincters, the thermal
dose in planes perpendicular to the urethra was examined at various spacings from the extremities of the transducer end-elements. Figure 26 shows the maximum thermal dose in these planes for all patients and two values of transurethral water cooling, $Tu$. Each sample point on the graph corresponds to one patient model, without distinction between patients with small or large ECD. The sample points have been slightly shifted to avoid visual overlap. For a $Tu$ of 37°C, the ultrasound transducer should be placed 4 mm and 3 mm away from the internal and external urinary sphincters, respectively, to avoid incurring thermal damage to these structures in all patients. Reducing $Tu$ to 22°C allows these margins to be reduced by 1 mm, to 3 mm and 2 mm for the internal and external urinary sphincters, respectively.

Protecting the urinary sphincters from thermal damage may lead to undertreatment of the prostate base and apex which must be carefully considered. The internal or involuntary urinary sphincter, located in the bladder neck is not considered essential in maintaining continence and is not preserved in conventional surgical removal of the prostate. Damage to the internal urinary sphincter may lead to retrograde ejaculation, but beyond affecting the patient’s reproductive ability, the impact on quality of life is negligible. Additionally, the incidence of prostate cancer is low at the prostate base [Grignon et al 1994]. As a result, the placement of the transducer relative to the bladder neck is probably not of primary concern in terms of safety or efficacy.

Conversely, the external or voluntary urinary sphincter located in the GUD plays a critical role in post-treatment urinary continence. The prostate apex is a common location of positive margins after surgery and may contain cancer [Grignon et al 1994]. Since, on the apex side, the margin of significant heating is about 2-3 mm from the transducer, the device must be well-positioned to avoid thermal damage to the external urinary sphincter while minimizing prostate undertreatment. A few mm of localized heating into the GUD could be clinically acceptable, because the GUD is on average about 1.33 cm thick (0.6-1.97 cm, n=25) containing
the external urinary sphincter and large levator ani muscles [McLaughlin et al]. Room temperature \( T_u \) would increase the protection of the external urinary sphincter.

Heating of the urinary sphincters was not significantly affected by the ultrasound frequency of the transducer end-elements, or by the ECD temperature.

![Graphs showing heating lateral to the ultrasound transducer during transurethral ultrasound prostate therapy. Each data point represents one patient and there is no distinction between those with a small or large ECD. The regions of reversible and irreversible damage as well as 240 EM43 are shown for reference. The results of using two urethral cooling temperatures are shown with offset points. (a) The maximum thermal dose reached outside the prostate base as a function of the distance from the last ultrasound transducer. (b) A similar graph for tissues outside the prostate apex. The extent of thermal damage is 1 mm greater at the prostate base, near the internal urinary sphincter. Reducing the urethral cooling temperature from 37°C to 22°C reduces the extent of thermal damage by 1 mm.]

3.3.6 Effect of perfusion and MR thermometry

Heating of the surrounding anatomy during transurethral ultrasound prostate therapy was affected primarily by the parameters discussed above. While the effect was very small, increasing the level of blood perfusion in the soft tissues decreased the thermal dose delivered to the surrounding structures. Increasing the soft tissue blood perfusion from 16 to 32 ml/min/100g reduced the irreversibly damaged rectum volume in 50% of the patients by 1-5 mm³, while there was no change in the other 50%. The same variation in blood perfusion had a minimal effect on the irreversible damaged volumes of the other structures. Higher blood
perfusion rates reduce tissue temperatures above 37°C more quickly yet increase treatment time; thus, the thermal dose delivered to the surrounding anatomy remains relatively unchanged.

The temperature uncertainty, temporal and spatial resolution of MR thermometry measurements, as well as the size of the ultrasound transducer elements can affect the treatment control and heating pattern generated in tissue [Chopra et al 2006, Pisani et al 2005]. These effects were not included in this study to isolate and understand only the thermal dynamics and consequent compromises involved in these treatments. Results from Chapter 2 indicate, however, that practical MR thermometry measurements do not affect heating of the rectum significantly; therefore, it is unlikely that it would have had an important impact on the heating of the surrounding anatomy in this study.

### 3.4 Conclusions

Regions of thermal coagulation shaped to human prostate geometries with MRI-guided transurethral ultrasound therapy were simulated and the thermal dose delivered to the rectum, pelvic bone, NVB and urinary sphincters was examined, for a wide range of 3D anatomical models obtained from images of prostate cancer patients. Numerical simulations incorporating multi-element transducer temperature feedback control showed that the prostate could be treated accurately; however, in the absence of treatment planning, some thermal impact could be predicted for the surrounding anatomy. Treatment strategies (the use of an appropriate size and temperature ECD, ultrasound frequency control and treatment margins) were investigated which could be used to reduce thermal injury to the surrounding anatomy. Accurate treatment of the posterior portion of the prostate was an important challenge because cancer is commonly located in that region and heating of the rectum posed the greatest risk to patient safety. The ECD size influenced strongly the heating of the surrounding anatomy: a large ECD (4.1mm in
diameter) reduced the heating to the NVB, while a small ECD (1.4mm in diameter) decreased the heating of the pelvic bone significantly and of the rectum slightly. Patient-specific treatment planning incorporating these numerical models could be used to optimize the inherent compromise between efficacy and safety. MRI-guided transurethral ultrasound therapy could potentially offer prostate cancer patients good local disease control and low complication rates.
4 Experimental Validation of Numerical Simulations and Demonstration of 3D Conformal MRI-guided Transurethral Ultrasound Prostate Therapy in Tissue-Mimicking Gel Phantoms‡‡

4.1 Introduction

Many studies have focused on the design, development and application of feedback algorithms to control the size, shape and degree of heating patterns for various ultrasound thermal therapy device configurations. In general, spatial control of the heated region is achieved by adjusting the location or orientation of the ultrasound beam as well as its intensity (power). In the context of high-intensity focused ultrasound (HIFU) therapy, where an elementary focal hot spot is created and scanned discretely across the region of interest, sophisticated feedback controllers have been described for creating areas of uniform temperature or thermal dose; however, the applications have been limited to single-point, linear or 2D planar control of the region of thermal coagulation [Arora et al 2006, Mougenot et al 2004, Vanne and Hynynen 2003, Lin et al 1990]. In 2009, Mougenot et al were the first to publish in-vitro and in-vivo heating results using 3D spatial and temporal temperature control with MRI-guided HIFU. Their target volumes, however, were limited to simple geometries (cubes and spheres) with volumes ≤ 2 cc. While the observed undertreated volumes were typically small (< 1% of the target volume, on average), overtreated volumes were large (> 60% of the target volume, on average).

In the context of intracavitary or interstitial ultrasound therapy, where the device is in direct contact with the treated tissue and the ultrasound beams are directional but unfocused, 

‡‡ This chapter is adapted from Burtnyk et al [2010b].
studies producing conformal regions of thermal coagulation have used manual adjustments of the ultrasound power [Kinsey et al 2008, Ross et al 2004] or automatic temperature feedback controllers, though limited to controlling temperatures at a single point or in 2D planes [Chopra et al 2005, Salomir et al 2006, Salomir et al 2009, Tang et al 2007, Chopra et al 2009]. In Chapter 2 the first feedback control algorithm to adjust automatically the rate of rotation and the ultrasound power and frequency of a moving ultrasound energy deposition field from multiple transducer elements was introduced in order to shape volumetric regions of thermal coagulation to predefined, complex, clinically-relevant 3D target boundaries (volumes ranged from 15 to 60 cc). While the treatment accuracy results were good (sum of the over- and undertreated volumes was less than 10% of the target volume), the study was theoretical in nature and the results were limited to numerical simulations.

The specific aim of this study was to demonstrate experimentally in well-characterized tissue-mimicking gel phantoms that 3D volumes of thermal coagulation could be shaped accurately and repeatedly to conform to clinically-relevant prostate geometries using a MRI-guided transurethral ultrasound device. Numerical simulations have been used extensively by our group to determine robust feedback control algorithms [Chopra et al 2005, Burtnyk et al 2009], optimal transducer designs [Kobelevskiy et al 2009], effects of various tissue and imaging parameters [Chopra et al 2006], as well as to evaluate potential targeting accuracy and safety in patient-specific anatomical models [Burtnyk et al 2009, Burtnyk et al 2010a]. While the basic simulations used to design the control algorithm have been validated [Chopra et al 2005, Chopra et al 2009], this study examined and quantified how accurately the 3D heating patterns predicted by the numerical simulations could be reproduced in well-controlled, tissue-mimicking gel phantom experiments.
4.2 Methods

Eleven 3D temperature feedback experiments were performed with an MRI-guided transurethral ultrasound prostate therapy system, five at 4.7 MHz on one patient model and six at 8.0 MHz on a second patient model. The accuracy and repeatability of these treatments were determined. The prostate models were derived from high resolution diagnostic MR images of prostate cancer patients, obtained with approval from the institutional research ethics board. Numerical simulations of the experiments, incorporating laser vibrometer measurements of transducer surface velocities, were performed to evaluate quantitatively how closely they predicted the heating patterns produced in a tissue-like homogeneous medium of well-known properties.

4.2.1 Experimental Setup

Heating experiments were executed using a MRI-compatible treatment delivery system developed within our research group, comprised of a multi-element ultrasound heating applicator, a rotational motor and radio-frequency (RF) electronics, as described in detail by Chopra et al [2008].

The ultrasound applicator housed an air-backed multi-element transducer, mounted on a rigid brass tube with outer diameter of 6.4 mm as seen in Figure 27a. The ultrasound transducer had a width of 3.5 mm and was sectioned into individual elements measuring 5 mm in length, for a good compromise between element size and MRI thermometry image thickness [Kobelevskiy et al 2009]. This study used two devices, with transducer fundamental frequencies of 4.7 and 8.0 MHz, and five or four individual elements respectively. A thin polyester membrane formed an acoustic window in the brass tube which allowed ultrasound to be transmitted into the gel phantom and enabled the device and transducer to be localized on T2-weighted MRI planning images (Figure 27b). To remove thermal losses and to couple
ultrasound into tissue, degassed water of temperature \( T_u (°C) \) flowed through the transurethral device.

Figure 27: a) Photograph of the 8.0 MHz multi-element transducer, mounted in a rigid brass tube forming the transurethral device, also referred to as the ultrasound applicator. The extent of the acoustic window is identified by the large white arrows. b) Sagittal T2-weighted MRI of the ultrasound applicator within a Zerdine gel phantom. The acoustic window is clearly visualized (large white arrows), the position of the transducer elements can be determined, the MRI thermometry images can be prescribed (rectangles), and the 3D target prostate boundary can be defined. The ultrasound applicator is parallel to \( B_0 \).

The ultrasound applicator was parallel to \( B_0 \) and mounted on a custom-machined rotational motor which used piezoceramic actuators (HR2, Nanomotion, Israel) and an optical encoder (Model LIA-20, Numerik Jena, Germany) to rotate the heating pattern continuously during treatment delivery. The ultrasound applicator was powered electrically through five independent channels consisting of a signal generator (WE7121, Yokogawa, Japan), RF amplifier (NP2910, NP Technologies, USA), bi-directional coupler (Pulsar Microwave, USA) and custom-made impedance matching network. The rotational motor and the power and frequency of each RF channel were monitored and controlled by a hardware-interface (HI)
computer which communicated with a treatment-delivery-interface (TDI) computer that calculated and analyzed the MRI thermometry images to implement the 3D feedback controller.

The heating experiments were performed in a homogeneous, Zerdine® polyacrylamide tissue-mimicking gel phantom (CIRS Inc., Norfolk, VA, USA) of known ultrasound and thermal properties: density, speed of sound, thermal conductivity and heat capacity are 1030 kg/m$^3$ [CIRS data sheet, 2010], 1540 m/s [CIRS data sheet, 2010], 0.56 W/m°C [Davidson and Sherar 2003] and 3.8 J/g°C [Davidson and Sherar 2003], respectively. The ultrasound amplitude attenuation of the Zerdine gel was measured to be $40 \pm 1.7$ Np/m at 4.7 MHz and $74 \pm 4.2$ Np/m at 8.0 MHz, resulting in the approximate relationship $\alpha_{att} = 6.45 \cdot f^{1.17}$, where $\alpha_{att}$ is the ultrasound amplitude coefficient (Np m$^{-1}$) and $f$ is the ultrasound frequency (MHz). These values were determined using the phase-insensitive method of total acoustic power insertion loss [Parker 1983], where a radiation force balance (Ohmic Instruments, Easton, MD, USA) measured the change in acoustic power resulting from the insertion of a Zerdine sample in the ultrasound path. Six different thicknesses of Zerdine gel were used, and the calculation of attenuation accounted for the water-gel intensity transmission coefficient and the ultrasound attenuation of water, but ignored the effects of multiple reflections which account for less than 0.1% of the acoustic power. The ultrasound absorption coefficient was determined by comparing in-vitro stationary heating patterns to those calculated using numerical simulations, as described subsequently.

The treatment planning and thermometry images were acquired using a standard quadrature head coil in a 1.5 T MRI (Signa, GE HealthCare, USA). Temperature images were calculated using the proton resonance frequency (PRF) method which relates changes in image phase to changes in temperature relative to a constant reference baseline [Ishihara et al 1995]. These temperature images were centered on each transducer orthogonal to the applicator (Figure
27b). Typical imaging parameters were: FSPGR (fast spoiled gradient echo), 4 or 5 slices, TE = 10 ms, TR = 69.2 ms, NEX = 1, FOV = 20 cm, slice thickness = 5 mm, image size = 128 x 64 pixels, bandwidth = 31.26 kHz, flip angle = 30°. The k-space data were zero-padded to 128 x 128 before calculating temperature. These parameters provided a voxel dimension of about 1.56 x 3.12 x 5.00 mm$^3$ (interpolated to 1.56 x 1.56 x 5.00 mm$^3$), an image acquisition time of 5 s (for all slices), and a temperature uncertainty of less than 0.5°C (standard deviation).

4.2.2 Control Algorithm

The feedback control algorithm used temperature and spatial anatomical measurements to modulate the device rotation rate, $\omega$ ($^\circ \text{min}^{-1}$), and the ultrasound power, $p_i$ (W), of each transducer element, $i = 1 \ldots n$, as described in Chapter 2. The goal of the control algorithm was to raise the temperature of the outer surface of a target volume to a critical threshold representative of thermal coagulation, $T_c$ ($^\circ \text{C}$), in one complete rotation of the applicator. A secondary objective of the control algorithm was to prevent temperatures within the coagulated volume from exceeding an upper limit, $T_h$, to avoid undesirable effects such as boiling.

The control algorithm modulated $\omega$ and $p_i$ based on the temperature difference between $T_c$ and $T_{r_i}$ ($\Delta T_{r_i} = T_c - T_{r_i}$), as well as the value of $r_i$. The control parameters were updated after every temperature measurement (5 s) and recalculated according to the following equations:
\[ \omega = \min_{i=1,n} \{ \omega_i \}, \]

\[ \omega_i = \begin{cases} 
\omega_{\min} & T_{\text{max}, i} > T_{\text{h}} \\
\omega_{\min} \leq \frac{k_\omega(i, r_i)}{\Delta T_r} \leq \omega_{\max}(r_i), T_{\text{max}, i} \leq T_{\text{h}} \text{ and } \Delta T_r > 0, \\
\omega_{\max}(r_i) & T_{\text{max}, i} \leq T_{\text{h}} \text{ and } \Delta T_r \leq 0 
\end{cases} \]

\[ p_i = \begin{cases} 
0 & T_{\text{max}, i} > T_{\text{h}} \text{ or } \Delta T_r \leq 0 \\
\frac{k_i(i, r_i) \cdot \Delta T_r}{p_{\max}} & T_{\text{max}, i} \leq T_{\text{h}} \text{ and } \Delta T_r > 0 
\end{cases} \]

where \( k_\omega(i, r_i) \) and \( k_p(i, r_i) \) were the rotational and power gain factors, respectively. These gain factors were determined as a function of target radius, \( r_i \), by performing a series of simple iterative simulations on circular target boundaries. The gain factors for the transducer end-elements \( (i = 1 \text{ or } n) \) were distinct to account for the different thermal dynamics when treating at the base and apex of the target prostate boundary.

**4.2.3 Heating Experiments**

Twenty-three heating experiments were performed using the system described above. For all experiments, the ultrasound applicator was inserted in the gel phantom at room temperature (at equilibrium with the environment), such that the baseline reference temperature of the thermometry images, \( T_b \), was approximately 22°C as measured using a needle thermometer. Using a 22°C baseline avoided unwanted temperature gradients which occurred with a 37°C gel phantom within a room-temperature MRI system. To avoid temperature gradients in the reference thermometry images, the temperature of the water flowing through the ultrasound applicator, \( T_u \), was adjusted to \( T_b \). The maximum acoustic power of each transducer element
was set to 1.75 W (time-average, continuous wave), sufficient to heat at large distances from the device without having $T_{max}$ exceed $T_h$ in the intervening gel.

Twelve stationary heating patterns (with no device rotation) were measured and compared with those calculated by numerical simulations, to estimate the ultrasound absorption coefficient of the Zerdine gel. For each device frequency of 4.7 and 8.0 MHz, six stationary heating patterns similar the one illustrated in Figure 28 were produced by setting the power of all transducer elements to $p_{max}$ for 120 s followed by a 60 s cooling period. The temperature distribution in a transverse plane located at the centre of the 20 or 25 mm ultrasound transducer array was recorded using the MRI thermometry parameters previously described, however with a 10 mm slice thickness to increase SNR. For each frequency, the six stationary heating patterns were then aligned and averaged to compare with those calculated using numerical simulations.

Figure 28: Typical stationary heating pattern produced in vitro, recorded in an axial plane, normal to the transducer surface, using MRI thermometry and scaled to $T_b = 37^\circ$C.

The remaining eleven heating experiments were full 3D treatments, where whole-gland human prostate volumes were targeted. Treatment repeatability using the 4.7 MHz device was
evaluated by performing five heating experiments all targeting the same prostate volume measuring 23 cc with target radius values, \( r_i \), ranging from 10 to 24 mm. Similarly, five heating experiments were performed using the 8.0 MHz device and an 11 cc target prostate volume with \( r_i \) from 8 to 18 mm. The target geometries were limited in volume due mainly to the small number of transducer elements available on each device (four or five 5 mm elements). Furthermore, ultrasound is quickly attenuated in gel or tissue at 8.0 MHz, reducing the maximum \( r_i \) that can be heated to \( T_c \) without having \( T_{max} \) exceed \( T_h \). Evaluating the performance of an 8.0 MHz device was appropriate for treating small prostates, targeted sub-volumes within the prostate, or for designing dual-frequency devices that can operate at two distinct frequencies [Chopra et al 2003]. Even though the largest target prostate volume in this study was 23 cc, simulations suggest that a 4.7 MHz device with seventeen 3 mm elements (or ten 5 mm elements) can treat large 60 cc prostate volumes accurately and safely [Burtnyk et al 2009, Burtnyk et al 2010a].

In vivo, the rectum is at risk of incurring thermal injury and it is therefore actively cooled using an endo-rectal cooling device (ECD) with water temperature \( T_{rect} (°C) \) [Nau et al 2004]. To study the protective effects of an ECD and to compare the thermal gradients generated by the ECD with those calculated by numerical simulations, a heating experiment was performed using the 8.0 MHz device and the 11 cc prostate volume in a special Zerdine gel phantom which included a water-cooled cylindrical cavity mimicking the effects of an ECD. The water temperature \( T_{rect} \) was adjusted to 10°C to approximate the in-vivo setting where \( T_b = 37°C \) and room temperature water is flowed through the ECD. The edge of the ECD was 19 mm from the centre of the ultrasound applicator and about 9 to 11 mm from the posterior prostate boundary, similar to human anatomy.

For all 3D temperature feedback experiments, the target temperature was set to \( T_c = T_b + 18°C \), corresponding to a critical temperature in vivo of \( T_c = 55°C \), representing acute thermal
coagulation [Chopra et al 2009]. Using $T_b = 22^\circ C$ and $T_c = 40^\circ C$ is physically equivalent (in a gel phantom) to the in-vivo situation with $T_b = 37^\circ C$ and $T_c = 55^\circ C$. The maximum device rotation rate, $\omega_{\text{max}}$, was restricted to 120°/min to avoid large angular increments and potential undersampling of the prostate boundary between feedback temperature measurements. The minimum non-zero device rotation rate, $\omega_{\text{min}}$, was set to 8°/min, slightly higher than the limitation imposed by the hardware.

### 4.2.4 Numerical Simulations

Simulations of MRI-guided transurethral prostate ultrasound therapy were performed according to the acoustic and thermal calculations presented in Chapter 2. Under the assumption of piston-like transducer vibration, $u_n$ is constant over the transducer surface and equal to $\sqrt{2W / \rho A}$, where $W$ is the time-averaged acoustic power (W) and $A$ is the transducer area ($m^2$) [Hynynen et al 1997b]. In reality, the transducer does not vibrate like a piston due to the presence of Lamb or surface waves, and the physical situation where the transducer is bound to a support frame on two of its edges. Because practical differences from theory propagate throughout the thermal calculations, an assumption of piston-like motion may not be sufficiently accurate. The normal surface velocity across transducer elements was measured, therefore, using a scanning laser vibrometer (PSV-400-M2-20, Polytec, Tustin, CA, USA) and incorporated into the acoustic pressure calculations. For each device frequency, the vibrometer measured the velocity as a function of time at a spatial resolution of 0.1 mm isotropic, directly on the surface of a transducer element submerged in water. In addition, the acoustic pressure along the centre axis of the transducer element was measured using a needle hydrophone (HP Series, Precision Acoustics LTD, UK) to compare with the result of the pressure calculations. The minimum separation distance between the transducer surface and the needle hydrophone was 9.5 mm to avoid temporal overlap between the measured signal of interest and the signal from electrical
The numerical simulation results presented in this paper were produced using the acoustic pressure fields calculated using the vibrometer velocity measurements.

The computational domain was a large 16 x 16 x 16 cm³ volume comprised of elements with Zerdine gel phantom properties. At $t = 0$, $T = Tb = 22°C$, and the thermal gradient at the computational domain boundary was set to zero.

The ultrasound transducer was modeled as a linear array of five, 3.5 x 5 mm rectangular elements, to match prototype devices used in this study. The space corresponding to a 3.5 mm radius transurethral applicator was held constant at $Tu$, approximating the conductive and convective cooling from a device with high water flow. To compare with the experiment including endorectal cooling, a subset of simulations was performed with the space corresponding to the ECD set to a constant temperature, $Trect = 10°C$.

Temperature measurements for feedback control using MR thermometry have limitations in spatial and temporal resolution and temperature accuracy, all of which affect treatment control and the heating pattern produced in tissue [Pisani et al 2005, Chopra et al 2006]. MRI-derived temperature feedback was modeled by spatially averaging the temperature into voxels, temporally averaging the temperature over the image acquisition time and by adding random zero-mean Gaussian noise to the temperature measurement. While the calculation domain was 1 mm isotropic, the temperatures used for feedback control were adjusted to a resolution equivalent to that of the MRI thermometry images: 1.56 x 3.12 x 5.00 mm³ voxel size, 5 s image acquisition time, and up to 0.5°C temperature measurement uncertainty (standard deviation).

The redistribution of energy due to scattering in the Zerdine gel has an important impact on the resulting heating pattern measured in vitro, reducing temperatures along the axis of ultrasound propagation and slightly increasing temperatures lateral to this dimension. One approach to account for the loss of energy due to scattering along the direction of ultrasound
propagation is to set the ultrasound absorption to a fraction of the attenuation, according to \( \alpha_{\text{abs}} = \Gamma \alpha_{\text{att}} \), where \( \Gamma \) is defined as the ultrasound absorption fraction and \( 0 < \Gamma \leq 1 \). Methods to determine the absorption or scattering coefficients usually rely on knowledge of the ultrasound pressure or intensity values [Wang et al 1999, Parker 1983], which cannot be readily measured within the gel phantom. Instead, the stationary heating patterns produced in vitro were compared (spatially and temporally) to those calculated by the numerical simulations to estimate the ultrasound absorption fraction of the Zerdine gel phantom. The value of \( \Gamma \) that provided the minimum absolute difference between the experimental and simulation results over the 120 s heating period was selected. The spatial redistribution of energy due to ultrasound scattering is complex and although it was not modeled in the numerical simulations, \( \Gamma < 1 \) implies a non-zero ultrasound scattering coefficient, \( \alpha_{\text{scatt}} \) (Np m\(^{-1}\)), equal to \( (1 - \Gamma)\alpha_{\text{att}} \).

Furthermore, \( \Gamma < 1 \) implies that the model violates conservation of energy, as a fraction of ultrasound energy equal to \( (1 - \Gamma) \) is removed from the system. To investigate the effect of \( \Gamma \), the numerical simulations of the 3D heating experiments were also performed with \( \Gamma = 1 \) (conservation of energy and no scattering).

### 4.2.5 Patient Models

Two realistic 3D prostate anatomical models were created by manually segmenting the prostate and urethra on high quality MR images of men with localized prostate cancer destined for radical prostatectomy. The multi-slice, axial, T2-weighted MR images were acquired using a 1.5 T MRI system (GE Signa Excite, Milwaukee, WI) with an 8-channel torso phased array surface coil, providing an in-plane voxel size of 0.78 mm and a slice thickness of 3 mm with no interslice gap. Because the images were acquired without a rigid transurethral device in place,
the traced boundaries were translated slightly to align the centre of the urethra to a common axis.

4.2.6 Evaluation Metrics

As described previously, the goal of the control algorithm is to raise the target prostate boundary to a temperature, \( T_c = T_b + 18^\circ C \). The treatment accuracy of the 3D gel experiments was determined by comparing spatially the target boundary to the \( T_c \) isotherm as calculated using 2D linear interpolation from the cumulative maximum temperature images of maximum temperature reached in each voxel throughout the treatment. The radial distance (spatial difference) between the \( T_c \) isotherm and target boundary sampled as a function of angle is one quantitative measure of treatment accuracy.

Of greater clinical significance is the volume of this spatial difference – i.e. the volume of prostate tissue that did not reach \( T_c \) (undertreatment) and the volume of tissue outside of the prostate which exceeded \( T_c \) (overtreatment). Since the \( T_c \) isotherm was interpolated from the MRI thermometry images, the treatment accuracy was limited by the in-plane voxel dimension. Differences between the target boundary and \( T_c \) isotherm of less than \( \pm \) half voxel were difficult to resolve accurately. The volume treatment accuracy was computed, therefore, by measuring the volume of the radial difference excluding \( \pm \) half voxel around the target boundary [Kobelevskiy et al 2009]. This meant that the volume treatment accuracy increased only when the \( T_c \) isotherm fell outside \( \pm \) half voxel of the target boundary. The in-plane voxel dimension was chosen as 2 mm which is approximately the average of the frequency and phase encode dimensions of the MRI thermometry images. Thus the volume treatment accuracy accumulated overtreatment only when the \( T_c \) isotherm extended beyond 1 mm from the target boundary and accumulated undertreatment only when the \( T_c \) isotherm fell short of the target boundary by more than 1 mm. The computation of the volumetric treatment accuracy assumed that the
spatial difference between the treatment and \( T_c \) isotherm boundaries was constant through the MRI thermometry slice thickness. In other words, the calculation considered the difference between the average \( T_c \) isotherm and the average target boundary within the thermometry slice. This is mathematically equivalent to calculating the true volumetric treatment accuracy with arbitrary \( T_c \) isotherm and target boundaries, assuming that these two do not cross within a given MRI thermometry slice. This assumption is reasonable because both the temperature distribution and the prostate shape vary smoothly and continuously, and are relatively constant over a 5 mm slice thickness.

The numerical simulations of the 3D heating experiments were compared to the average experimental result by examining how well they predicted treatment accuracy, treatment safety and treatment time. For treatment accuracy, the locations of the \( T_c \) isotherms (mm), linearly interpolated from the maximum temperature distributions, were compared. A first-order measure of how well the simulations predicted treatment safety was obtained by comparing the distance between the \( T_c \) and \( T_c - 5^\circ C \) isotherms, defined as \( d_{\Delta T=5} \) (mm), a simple measure of the temperature gradient extending beyond the target prostate boundary into the surrounding anatomy. A 5°C temperature gradient was selected as corresponding roughly to the onset of acute and late thermal injury in the normal anatomy outside the prostate for the acute and late coagulation temperatures \( T_c = 55^\circ C \) and \( 52^\circ C \), respectively [McDannold et al 2000]. The maximum temperature distributions accumulated over each thermometry image inside and outside the target prostate boundary were also compared to provide an overall sense of how well the simulations predicted the in-vitro heating patterns, another measure of treatment safety. Comparing the temperatures inside and outside the target boundary evaluated how well the simulations predicted, respectively, the areas where \( T_{max_i} \) approaches \( T_h \), and the temperature distribution within the surrounding normal anatomy. To assist this comparison, two regions of interest (ROI) were defined to exclude areas close to the ultrasound applicator where
susceptibility artifacts can interfere with temperature and areas outside the gel phantom where the MRI phase signal is random. The first ROI extended 8 mm radially from the ultrasound applicator centre to the prostate boundary, and the second ROI extended from the prostate boundary to a distance of 40 mm from the ultrasound applicator centre. Finally, the experiment treatment times were compared to the numerical simulation predictions.

4.3 Results and Discussion

4.3.1 Acoustic Pressure

The transducer velocity profile measured using the scanning laser vibrometer did not match that of a piston. Under the assumption of piston-like motion, the velocity amplitude of a 3.5 x 5 mm$^2$ transducer element (any frequency) operating at 1 W acoustic in water is about 0.28 m/s, constant across its surface. The scanning laser vibrometer measured velocities more than twice this value at the centre of the transducer reducing to almost zero at the transducer edges. Figure 29a and Figure 29b show the transverse acoustic pressure distribution calculated for a 4.7 MHz transducer element operating at 1 W acoustic in water, using, respectively, the vibrometer velocity measurements and assumption of piston-like motion. The differences were most noticeable in the near-field of the pressure distributions and were increasingly averaged with distance from the transducer. The near-field pressures were higher for the vibrometer velocity measurements due to higher local velocities near the centre of the transducer. The fine interference pattern lateral to the main beam was reduced using the vibrometer measurements due to the non-constant velocity profile of the transducer. The distance to the near-field/far-field transition was reduced slightly for the vibrometer measurements because the effective size of the transducer is smaller due to near-zero vibration at the transducer edges. The far-field of
the pressure distributions were similar, shifted slightly due to the change in location of the near-field/far-field transition.

Laser vibrometer measurements in water are susceptible to artifacts generated by changes in refraction index due to variations in pressure in water along the optical path of the scanning laser, a phenomenon termed acousto-optic interactions. Morosov [2006] studied this effect and concluded that the displacement observed by the vibrometer is a combination of the real transducer vibrational modes and a structure of acousto-optic distortions caused by the interference of waves in water. Moreover, Morosov showed that the period of the acousto-optic distortions is equal to the wavelength of the transducer frequency in water. Acousto-optic distortions were observed in our measurements, but only in the case of the 4.7 MHz transducer, along the 3.5 mm dimension. The interference pattern repeated itself eleven times over 3.5 mm, yielding a period equal to the wavelength of the transducer frequency in water. The acousto-optic distortions were not observed in the transducer dimension measuring 5 mm, possibly because the effective size of the laser focus was not circular and was larger in that dimension, thus spatially averaging fine differences. Furthermore, acousto-optic interactions were not observed when measuring the velocity of the 8.0 MHz transducer elements because the period of the interference pattern was smaller than the scanning laser focal spot. Despite the presence of minor artifacts caused by acousto-optic interactions, the vibrometer measurements provided a solid foundation for the acoustic pressure calculations because: 1) the vibrometer measurements provided a much better representation of the true transducer vibration compared to the assumption of piston-like motion, 2) the largest errors occur close to the transducer surface, within the ultrasound applicator tube, where the exact pressure values have little effect on the resulting calculated heating distribution in gel, and 3) the fine interference pattern was averaged out quickly as the pressure was calculated at increasing distance from the transducer.
In addition, the pressure calculations of Figure 29a and Figure 29b were compared to normalized acoustic pressure measurements using a needle hydrophone (Figure 29c). The pressure calculations using the vibrometer measurements represented very closely the hydrophone-measured pressure distribution, and the acousto-optic distortions had little impact in the region of interest.

![Figure 29](https://example.com/figure29)

Figure 29: Acoustic pressure calculations and measurements. (a) and (b) show the transverse acoustic pressure distribution calculated for a 4.7 MHz transducer element operating at 1 W acoustic in water using, respectively, the vibrometer velocity measurements and the assumption of piston-like motion. Differences are most noticeable in the near-field of the pressure distributions. (c) The pressure calculations from a) and b) were compared to normalized acoustic pressure measurements using a needle hydrophone. The pressure calculations using the vibrometer data represent very closely the measured pressure distribution. The range of distances from the transducer (8-40 mm) which are of interest for heating control are indicated.

### 4.3.2 Stationary Heating Patterns: Determining the Ultrasound Absorption Coefficient of the Zerdine Gel Phantom

Numerical simulations of the stationary heating patterns produced in vitro were performed with the absorption fraction, $\Gamma$, varied from 0.5 to 1 in increments of 0.05 ($\alpha_{abs} = \Gamma \alpha_{att}$). For both device frequencies, 4.7 and 8.0 MHz, $\Gamma = 0.70$ provided the minimum difference between the experimental and simulated heating patterns, spatially across the entire thermometry image and temporally over the 120 s heating period. This absorption fraction is towards the lower end of the range of values reported in literature for agar-based gel, $\Gamma = 0.75$ [Chin et al 1990], and fresh liver, $\Gamma = 0.66$ to 0.97 [Pauly and Schwan 1971, Hill et al 1978, Nicholas et al 1982, Parker...
1983, Nassiri and Hill 1986], which the Zerdine gel is intended to mimic. Figure 30 compares the experimental and simulated heating patterns, scaled to $T_b = 37^\circ$C: Figure 30a and Figure 30b show the temperature along the direction of heating at the centre of the transducer at 30 and 90 s, and Figure 30c and Figure 30d show the temperature lateral to the direction of heating at 10 and 20 mm from the transducer after 90 s of heating. As expected, for similar heating times, the 8.0 MHz temperature profiles had a higher $T_{\text{max}}$, with the temperatures reducing to $T_b$ within a shorter distance from the transducer. Along the direction of heating, the simulated temperatures using $\Gamma = 0.70$ matched closely the profiles obtained in the Zerdine gel phantom, including the sharp temperature gradient near the ultrasound applicator. The simulations predicted, however, a slightly narrower heating pattern lateral to the direction of heating because the redistribution of ultrasound energy due to scattering was not considered in the calculations. This could have some impact on the numerical simulations of 3D treatments where the underheated gel lateral to the direction of heating will eventually lie within the direction of heating due to the continuous rotation of the ultrasound applicator. Initial simple approaches to stretch or blur the acoustic fields were attempted; however, the results were not changed.

Overall the simulations using $\Gamma = 0.70$ predicted with good accuracy the stationary heating patterns produced in vitro: for the 4.7 and 8.0 MHz devices, respectively, the mean ± stdev [min, max] temperature difference is $0.23 \pm 0.56 [-0.91, 2.3]$ °C and $0.32 \pm 0.86 [-1.1, 5.2]$ °C, the $T_c$ isotherm difference is $0.29 \pm 0.44 [-0.29, 1.2]$ mm and $0.10 \pm 0.19 [-0.23, 0.52]$ mm, and the $d_{\Delta T=5}$ difference is $0.22 \pm 0.25 [-0.21, 0.57]$ mm and $0.17 \pm 0.18 [-0.12, 0.45]$ mm.

Setting $\Gamma = 1.0$, the temperatures of the stationary heating patterns were consistently overestimated by the simulations: for the 4.7 and 8.0 MHz devices, respectively, the mean ± stdev [min, max] temperature difference is $3.9 \pm 3.9 [0.11, 16.4]$ °C and $3.7 \pm 5.4 [-0.10, 25.1]$ °C, the $T_c$ isotherm difference is $4.6 \pm 0.53 [4.0, 5.7]$ mm and $2.6 \pm 0.27 [2.2, 3.3]$ mm. The $d_{\Delta T=5}$ difference, however, remained comparable to the results obtained with $\Gamma = 0.7.$
Figure 30: Comparison of experimental and simulated stationary heating patterns to determine the ultrasound absorption coefficient of the Zerdine gel phantom. The graphs have been scaled to $T_b = 37^\circ\text{C}$ to represent the temperature distribution expected in vivo. (a) and (b) show the temperature along the direction of heating at the centre of the transducer at 30 and 90 s. (c) and (d) show the temperature lateral to the direction of heating at 10 and 20 mm from the transducer after 90 s of heating (identified with arrows on a) and b). MRI temperature measurements could not be made within the transurethral device (shaded region). For similar heating times, the 8.0 MHz temperature profiles have a higher $T_{\text{max}}$ and temperatures reduce closer to $T_b = 37^\circ\text{C}$ within a shorter distance from the transducer. Along the direction of heating, the simulated temperatures using $\Gamma = 0.70$ match closely the profiles obtained in the Zerdine gel phantom, including the sharp temperature gradient near the ultrasound applicator. The simulations predict, however, a slightly narrower heating pattern lateral to the direction of heating because the redistribution of ultrasound energy due to scattering was not considered in the calculations.

4.3.3 3D Temperature Feedback Experiments: In-Vitro Results

Treatment accuracy results of the ten MRI-guided 3D temperature feedback experiments are summarized in Figure 31. For all experiments at both frequencies, the mean ± standard deviation of the radial treatment accuracy was comparable to the in-plane voxel dimension of the MRI thermometry images from which the $T_c$ isotherm was interpolated (Figure 31a and Figure 31c). In general, the $T_c$ isotherm slightly exceeded the target boundary. The maximum and minimum radial treatment accuracy usually remained within ±2 mm. The volumetric
treatment accuracy of the experiment average (worst-case) was 0.18 cc (0.56 cc) or 0.8 % (2.5%) of the prostate volume for the 4.7 MHz experiments and 0.24 cc (0.80 cc) or 2.1% (7.3%) of the prostate volume for the 8.0 MHz experiments. These results demonstrate the high degree of accuracy that can be achieved in 3D using relatively simple multi-slice MRI temperature feedback control.

Figure 31: Treatment accuracy (radial and volumetric) of all 3D in-vitro experiments. (a) and (c) show the radial treatment accuracy for the 4.7 and 8.0 MHz experiments, respectively, along with the result of the experiment average. The mean ± standard deviation of the radial treatment accuracy is comparable to the in-plane voxel dimension of the MRI thermometry images (X Res. and Y Res. are the frequency and phase encode directions, respectively). (b) and (d) show the volumetric treatment accuracy, which remained well below 0.5 cc (2.2% of the prostate volume) for the 4.7 MHz experiments and 0.8 cc (7.5% of the prostate volume) for the 8.0 MHz experiments.
The average (range) treatment times for the 4.7 and 8.0 MHz experiments were, respectively, 20.9 min (18.2 to 23.8 min) and 20.6 min (18.6 to 21.9 min). The treatment accuracy values remained relatively constant compared to the treatment times indicating that the feedback controller was successful in adjusting the treatment delivery in response to many variations in experimental setup. Such variations include precise location of the ultrasound applicator and transducer elements, alignment of the MRI thermometry images versus the transducer elements, precise determination of the ultrasound beam direction [Chopra et al 2006], changes in transducer performance or efficiency, having $Tu$ set exactly to $Tb$ within the MRI bore, fluctuations in SNR, and MRI phase drift.

The treatment accuracy results of the 8.0 MHz experiments had more variability than the ones at 4.7 MHz. This was likely due to the fact that the 8.0 MHz experiments were performed before the 4.7 MHz experiments and variables such as the precise localization of the ultrasound applicator and transducer elements were not as well controlled.

The sizes of the target volumes were limited primarily by the number of transducer elements available on the devices, as opposed to issues related to the treatment delivery system or the feedback control algorithm. We selected from our database of 40 models, the patients with the largest prostate volumes satisfying the 20 or 25 mm restriction on prostate length. (Ten patients had a prostate length of 28 mm or less, all with volumes less than 23 cc). The 3D temperature feedback controller implemented in this study could easily be extended for devices with additional transducer elements, enabling larger prostate target geometries to be treated without increasing treatment time. These devices, however, would require more thermometry images per acquisition time and some MRI parameters (spatial, temporal, SNR) might have to be adjusted. Alternatively, using a 3.0 T MRI system would enable experiments using devices with more than five transducer elements, with improvements in MRI parameters. Early experience at 3.0 T has shown that nine thermometry images can be acquired in 7 s with similar
or better resolution than has been reported here. Additionally, susceptibility artifacts from the transurethral device at 3.0 T are spatially limited and are likely to not interfere with the temperature feedback measurements required by the control algorithm.

4.3.4 3D Temperature Feedback Experiments: Accuracy of Numerical Simulations

The accuracy with which the numerical simulations predicted the $T_c$ isotherm, $d_{\Delta T=5}$, overall maximum temperature distribution, and treatment time is summarized in Table 9 for $\Gamma = 0.70$ and $\Gamma = 1.0$. Additionally, the overall maximum temperature distribution produced in vitro and predicted by the numerical simulations with $\Gamma = 0.70$ are compared at mid-prostate in Figure 32 and near the end of the prostate in Figure 33 (prostate base for 4.7 MHz and prostate apex for 8.0 MHz). The color scale has been set such that the $T_c$ isotherm (55°C for $T_b = 37^\circ$C) can be visualized as the boundary at the yellow-cyan transition. The experimental MRI thermometry images have been linearly interpolated to 1 mm isotropic to match the spatial resolution of the simulations, facilitating visual comparison. Subtracting the experimental thermometry images from the simulations (for example subtracting Figure 32a from Figure 32b) and applying the ROI masks discussed previously, generates the difference in maximum temperature distribution inside and outside the target prostate boundary, summarized in Table 9.

Figure 32 and Figure 33 together with Table 9 demonstrate that with $\Gamma = 0.70$, the numerical simulations predicted with high accuracy the shape and extent of the $T_c$ isotherm as well as the maximum temperatures reached within and the thermal gradient extending beyond the target prostate boundary. In fact, the simulations predicted the result of the average experiment within the variability observed between experiments (except treatment time). In all cases, the $T_c$ isotherm and $d_{\Delta T=5}$ were predicted usually to within ± half voxel, and in the worst case to within ± voxel.
Figure 32: The maximum temperature distributions measured in vitro and those predicted by the numerical simulations with $\Gamma = 0.70$ at mid-prostate, scaled to $T_b = 37^\circ$C. The temperature scale has been set such that the $T_c$ isotherm (55°C for $T_b = 37^\circ$C) can be visualized as the yellow-cyan transition boundary. The experimental MR thermometry images have been linearly interpolated to 1 mm isotropic to match the spatial resolution of the simulations, facilitating visual comparison. Subtracting the experimental thermometry images from the simulation (for example subtracting a) from b) results in the maximum temperature distribution difference, summarized in Table 9. The simulations predict with a high level of accuracy the extent, shape and temperature of the heating patterns.
Figure 33: The maximum temperature distributions measured in vitro and those predicted by the numerical simulations with $\Gamma = 0.70$ near the end of the prostate (prostate base for 4.7 MHz and prostate apex for 8.0 MHz). Similarly to Figure 32, the images have been scaled to $T_b = 37^\circ C$, interpolated to 1 mm isotropic and the color scale set such that the $T_c$ isotherm can be visualized as the yellow-cyan transition boundary. While the simulations predict with a high level of accuracy the extent, shape and temperature of the heating patterns, the amount of overtreatment is slightly overestimated near the end of the prostate compared to the results at mid-prostate (Figure 32).

Setting the ultrasound absorption coefficient equal to the attenuation coefficient ($\Gamma = 1.0$) maintained the accuracy with which the simulations predicted the $T_c$ isotherm, the $d_{\Delta T=5}$, and the maximum temperature distribution outside the prostate boundary. This is due to the temperature feedback controller compensating for differences in ultrasound absorption as well as the similar temperature gradients extending beyond $T_c$ with $\Gamma = 0.7$ and 1.0 observed during the simulated stationary heating patterns. As expected, however, using $\Gamma = 1.0$ increased the maximum
temperatures predicted by the simulations within the prostate boundary, leading to differences of up to 14°C near the transurethral device.

The accuracy of the $T_c$ isotherm predicted by the numerical simulations was slightly different when comparing the result of the transducer end-elements to the other non-end-elements (referred to as middle-elements). While the standard deviation of the difference between the $T_c$ isotherm predicted by the simulations and the one measured in vitro was consistent across all transducer elements, the mean of this difference was always slightly larger for the transducer end-elements. This suggests that the Zerdine thermal conductivity may have been underestimated in the simulations, which would also theoretically improve the agreement between the experimental and simulated stationary heating patterns in the lateral dimension (Figure 30c and Figure 30d). This effect is not due to physical differences in end-element behavior, as the laser vibrometer measurements were very similar for all transducer elements within a device. Quantitatively, comparing the results of the transducer end-elements to the middle-elements, the mean difference between the $T_c$ isotherm predicted by the simulation and the one measured in vitro increased from about 0.2 to 1.0 mm and from about -0.4 to 0.4 mm, for the 4.7 and 8.0 MHz experiments, respectively.

With $\Gamma = 0.70$, the simulations predicted a treatment time on average 6.8 min (33%) longer and 2.9 min (14%) shorter than obtained in the Zerdine gel phantom for the 4.7 and 8.0 MHz experiments, respectively. These discrepancies are probably due to the combination of the prostate radii distribution of each target boundary and the heating characteristics observed in Figure 30 with $\Gamma = 0.70$. The larger the prostate radius, the longer the heating time and the more the temperatures are underestimated lateral to the direction of heating. The 4.7 MHz experiments treated a larger target prostate boundary with a median prostate radius of 16 mm (range of 10 to 24 mm). Over this range of radii, Figure 30a shows that the temperatures are predicted accurately along the direction of heating. As the ultrasound applicator rotates,
therefore, the simulations will underestimate the temperature lateral to the direction of heating, slowing the treatment. In fact, the simulations with \( \Gamma = 0.70 \) effectively remove 30% of the energy delivered to the virtual gel phantom, in agreement with the predicted treatment time being 33% longer than obtained during the 4.7 MHz experiments. When \( \Gamma = 1.0 \) and no energy is removed from the system, the simulations predict the treatment time with good accuracy at 4.7 MHz, within 0.6 min or 3%.

The 8.0 MHz experiments targeted a prostate target boundary that was much smaller, with half of the prostate radii lying within 8 to 12.5 mm from the transducer; thus, temperatures lateral to the direction of heating were underestimated less significantly. As seen in Figure 30b, over the range of 8 to 12 mm and at 8.0 MHz, the simulations tended to overestimate the temperatures along the direction of heating. Together, these considerations could explain why the treatment time was overestimated at 4.7 MHz and underestimated at 8.0 MHz. Additionally, the variability in treatment times achieved experimentally is an indication that there could be other factors affecting the heating and temperature feedback in vitro that are not considered by the simulations. Some of these factors have already been discussed, such as the slight misalignment of the thermometry images with the ultrasound transducer elements. Another possibility is related to the Zerdine gel properties which potentially change with temperature, a factor not accounted for in the acoustic and thermal calculations. Also, non-linear ultrasound propagation within the gel phantom could contribute to some of the differences observed between the simulations and experiments, as the ultrasound pressure calculations used linear acoustics. Additionally, the effect of MRI susceptibility artifacts generated by the rotating ultrasound applicator and transducer were not considered by the simulations. These tend to produce angle-dependent negative temperature errors close to the device (errors of 1°C to 3°C for \( r_i < 10 \text{ mm} \)). There are no susceptibility artifacts at the beginning of the treatment when the ultrasound applicator is in the same position as it was during the acquisition of the reference
thermometry image; however, susceptibility artifacts become more important as the device rotates, reaching maximum effect when the ultrasound applicator is 180° from its initial position. When targeting small prostate radii, such as in the case of the 8.0 MHz experiments, susceptibility artifacts could contribute to longer treatment times in-vitro.

Table 9: Quantifying the accuracy with which the simulations predicted the $T_c$ isotherm, $d_{AT-5}$, maximum temperature distribution and treatment time of the 3D in-vitro experiments, for $\Gamma = 0.70$ and $\Gamma = 1.0$. The differences were calculated by subtracting the experimental result from the simulation.

<table>
<thead>
<tr>
<th>Difference: Sim – Expt</th>
<th>Average 4.7 MHz Experiment</th>
<th>Average 8.0 MHz Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± stdev</td>
<td>max</td>
</tr>
<tr>
<td>$\Gamma = 0.70$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c$ isotherm difference (mm)</td>
<td>0.5 ± 0.4</td>
<td>2.1</td>
</tr>
<tr>
<td>$d_{AT-5}$ difference (mm)</td>
<td>-0.02 ± 0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Max. temperature distribution difference within the prostate (°C)</td>
<td>0.6 ± 1.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Max. temperature distribution difference outside the prostate (°C)</td>
<td>0.6 ± 0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Treatment time difference (min)</td>
<td>6.8</td>
<td>9.6</td>
</tr>
<tr>
<td>$\Gamma = 1.0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c$ isotherm difference (mm)</td>
<td>1.1 ± 0.3</td>
<td>2.8</td>
</tr>
<tr>
<td>$d_{AT-5}$ difference (mm)</td>
<td>-0.2 ± 0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Max. temperature distribution difference within the prostate (°C)</td>
<td>4.0 ± 2.2</td>
<td>11.2</td>
</tr>
<tr>
<td>Max. temperature distribution difference outside the prostate (°C)</td>
<td>1.0 ± 0.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Treatment time difference (min)</td>
<td>0.6</td>
<td>3.4</td>
</tr>
</tbody>
</table>
4.3.5 3D Temperature Feedback Experiments: ECD Cooling

The protective cooling effect generated by an ECD was investigated using the 8.0 MHz device and the 11 cc target prostate boundary (identical to the 8.0 MHz experiments described previously). Cold water flow to the ECD was initiated after the acquisition of the reference thermometry image in order to ensure a constant room temperature $T_b$ across the Zerdine gel phantom. Due to a design flaw in the gel phantom container incorporating an ECD, however, pressure changes upon initiation of flow often created motion artifacts near the ECD. One successful 3D in-vitro experiment with ECD is reported here.

Figure 34a and Figure 34b show the cumulative maximum temperature reached at each voxel throughout the 8.0 MHz experiment, without and with ECD cooling, respectively. The heating patterns and treatment accuracy are very similar, with the exception of the cooling effect from the ECD near the posterior prostate and bottom of Figure 34b. (As a side note, comparing Figure 34a and Figure 34b also shows how the chosen location of the ultrasound applicator centre could vary, one factor contributing to the variability between experiments as discussed previously.) The experiment with ECD cooling resulted in a radial treatment accuracy of (mean ± stdev [min, max]) 1.1 ± 0.8 [-1.2, 2.8] mm and a volumetric treatment accuracy of 0.6 cc, almost entirely overtreatment, similar to the results obtained without an ECD.

The temperature distribution extending radially from the centre of the ultrasound applicator through the centre of the posterior prostate (dashed arrow in Figure 34a and Figure 34b) is shown along with the numerical simulation predictions in Figure 34c and Figure 34d for the thermometry images associated to the middle and end elements, respectively. Temperature measurements in the ECD and applicator (flowing water) were not accurate and are not shown. The distance to the target prostate boundary (the prostate radius) is also indicated.
Figure 34: The heating patterns produced in the Zerdine gel phantom without (a) and with (b) ECD cooling. They are very similar, with the exception of the cooling effect from the ECD near the posterior prostate and near the bottom of B. The temperature distribution extending radially from the centre of the ultrasound applicator (dashed arrow in a) and b) along with the numerical simulation predictions are shown for the thermometry images associated to the middle (c) and end (d) elements. The distances corresponding to the transurethral device and ECD are identified, as MRI temperature measurements in these regions are not accurate. The distance to the target prostate boundary (the prostate radius) is also indicated. The numerical simulations predict accurately the temperature gradient produced by the ECD.

Several interesting observations arise from Figure 34. First, despite the strong cooling effect produced by the ECD, treatment accuracy was similar for both experiments demonstrating the strength of using temperature feedback to control treatment delivery. The treatment time of the gel phantom experiment with ECD cooling was 35 s longer than the one without, consistent with increased energy delivery to the posterior prostate. The device rate of rotation near the
posterior prostate is already rapid due to very short target radii and this small increase in treatment time observed experimentally is consistent with the numerical simulations which predicted an increase of 32 s.

Second, cooling from the ECD reduced the heating within the virtual rectum significantly. While the temperature difference at the $Tc$ isotherm is zero (by definition and to preserve treatment accuracy), the ECD can reduce temperatures by up to 8°C within the virtual rectal wall, offering significant thermal protection.

Third, the maximum temperatures $T_{max_i}$ were overestimated by the numerical simulations by about 2 to 4°C for both the middle and end transducer elements. While a component of the overestimation was probably caused by inaccuracies in the numerical simulations as observed for short radii in Figure 30b, the majority of the difference was most likely due to effects from rotational susceptibility artifacts as discussed previously.

Lastly, the numerical simulations predicted with high accuracy the strong temperature gradient produced by the ECD in vitro, with a slight underestimation, on average, by about 0.7°C (maximum difference of 2°C). Figure 34 illustrates the validity and the strength of using simulations to investigate thoroughly the effects of these treatments on the rectal tissues, as well as to design treatment delivery strategies to protect the rectum from incurring thermal damage [Burtnyk et al 2010a].

4.4 Conclusions

This study demonstrated experimentally that 3D volumes of thermal coagulation can be shaped accurately and reproducibly to clinically-relevant human prostate geometries in a tissue-mimicking gel phantom, using a transurethral ultrasound device and MRI temperature feedback control. In all cases, a high degree of treatment accuracy was achieved, comparable to the
spatial resolution of the MRI thermometry images. This study also demonstrated the high accuracy with which numerical simulations can predict the 3D heating pattern produced in a well-characterized Zerdine gel phantom. These predictions could only be made so accurately because of the incorporation of measured transducer vibration characteristics as well as the characterization of the gel ultrasound absorption fraction. This work supports the use of these validated simulations as an effective treatment planning tool and to investigate the efficacy and safety of treatment delivery strategies.
5 Conclusions and Future Directions

MRI-guided transurethral ultrasound prostate therapy is being developed as a minimally-invasive treatment for men with localized prostate cancer, potentially offering good local disease control and low complication rates. The ability to produce conformal patterns of thermal coagulation using temperature feedback and a single rotating rectangular transducer element (2D treatment) has been demonstrated in vivo [Chopra et al 2009]; this thesis explores and addresses the challenges of producing 3D conformal regions of thermal coagulation shaped to whole-gland prostate volumes while limiting the thermal impact to the surrounding important anatomy.

Regions of thermal coagulation shaped to human prostate geometries with MRI-guided transurethral ultrasound therapy were simulated and the thermal dose delivered to the rectum, pelvic bone, NVB and urinary sphincters was examined, for a wide range of 3D anatomical models obtained from images of prostate cancer patients. Numerical simulations incorporating a new multi-element transducer 3D temperature feedback controller showed that a high degree of treatment accuracy was achieved over a variety of prostate geometries representative of patients who would be considered for this type of therapy. In the absence of treatment planning, however, some thermal impact could be predicted for the surrounding anatomy. Treatment delivery strategies were developed and investigated (the use of an appropriate size and temperature ECD, ultrasound frequency control and treatment margins), and simulations showed that they could be used to reduce thermal injury to the surrounding anatomy. Accurate treatment of the posterior portion of the prostate was an important challenge because cancer is commonly located in that region and heating of the rectum posed the greatest risk to patient safety. The ECD size influenced strongly the heating of the surrounding anatomy: a large ECD (4.1 mm in diameter) reduced the heating to the NVB, while a small ECD (1.4 mm in diameter)
decreased the heating of the pelvic bone significantly and of the rectum slightly. Patient-specific treatment planning incorporating these numerical models could be used to optimize the inherent compromise between efficacy and safety.

Experiments showed that 3D volumes of thermal coagulation can be shaped accurately and reproducibly to clinically-relevant human prostate geometries in a tissue-mimicking gel phantom, using a transurethral ultrasound device and MRI temperature feedback control. In all cases, a high degree of treatment accuracy was achieved, comparable to the spatial resolution of the MRI thermometry images. The results of these experiments were also used to demonstrate the high accuracy with which the numerical simulations can predict 3D heating patterns produced in a well-characterized Zerdine gel phantom. This work supports the use of these validated simulations as an effective treatment planning tool and to investigate the efficacy and safety of treatment delivery strategies. MRI-guided transurethral ultrasound therapy could potentially offer prostate cancer patients good local disease control and low complication rates.

While this thesis developed complete 3D treatment delivery strategies and demonstrated the feasibility of producing 3D volumes of thermal coagulation for the safe and effective treatment of prostate cancer using a MRI-guided transurethral ultrasound device, in-vivo evaluation of this therapy remains an important challenge before clinical use. Some of the issues associated with in-vivo treatments which cannot be examined in vitro include: the effect of blood perfusion (and its dynamics in response to the therapy), partial volume effects from adipose tissue within voxels where temperature measurements are of interest, organ and tissue motion during treatment, and MRI baseline phase drift. The expected effect of blood perfusion in vivo has been examined in the simulation studies included in this thesis, however, the assumptions used were somewhat simplistic due to the fact that prostate blood perfusion dynamics are not well characterized and difficult to determine a priori.
The delivery of ultrasound energy in the prostate relies on accurate MRI temperature measurements used for feedback control. Techniques to correct partial volume effects and baseline drift should be implemented and evaluated in vivo. Partial volume effects can be avoided by using temperature measurements well-within the prostate gland (away from the periphery near adipose tissue) or by using fat-suppression MRI sequences [Zwart et al 1999]. Baseline drift can be corrected easily by monitoring the phase in a non-heated region of the image, assuming that the drift is constant spatially across each image. If the baseline drift varies temporally and spatially, more complex non-linear approaches are necessary [Grimault et al 2004, El-Sharkawy et al 2006]. Finally, while organ or tissue motion does not typically interfere with the MRI temperature measurements of interest (within the prostate), techniques to correct motion artifacts or to identify regions where motion artifacts are significant should be implemented and evaluated in vivo.

Beyond the in-vivo evaluation of this therapy, the development of more accurate anatomical patient models, the validation of the acoustic and thermal calculations in bone, and the improvement of the 3D temperature feedback control algorithm are areas of future research. First, the anatomical images of prostate cancer patients used in this thesis did not include the rigid transurethral device which modifies the shape of the prostate and its position relative to the surrounding important structures. MRI images of eight patients with the transurethral device in place have been acquired recently as part of a proof-of-principal clinical trial at Sunnybrook Health Sciences Centre, ongoing since July 2009. These images reveal that the insertion of the transurethral device modifies the location of the urethra within the prostate, shifting it towards the anterior portion of the gland, away from the rectum. While the conclusions of this thesis are unlikely to change, additional simulations examining treatment accuracy and safety in these patient models are warranted. Second, while the acoustic and thermal calculations have been validated in a tissue-mimicking gel (soft-tissue), the assumptions used when modeling
ultrasound interaction with bone should also be verified experimentally. The assumptions used in this thesis were set to provide an estimate of the worst-case bone heating; more accurate models could be used to better inform the choice of ultrasound frequency for these treatments. Finally, the 3D feedback temperature control algorithm developed in this thesis is the first adjust automatically the rate of rotation and the ultrasound power and frequency of a moving energy deposition field from multiple transducer elements in order to shape volumetric regions of thermal coagulation to predefined complex 3D target boundaries. The control algorithm performs well in simulation and in vitro, where the tissue properties are well-known and the feedback temperature measurements are accurate. In-vivo, dynamic attenuation and perfusion changes outside the expected range of values as well as very noisy feedback temperature measurements can compromise treatment accuracy and safety. The development of a model-based controller which incorporates patient-specific measurements of tissue properties [Vanne and Hynynen 2003, Huttunen et al 2006, Cheng and Plewes 2002, Wang et al 1999] and filtering techniques to reduce the amount of noise in the temperature measurements could improve treatment delivery.

Focal therapy of prostate cancer, where only subvolumes containing cancer within the prostate are targeted as opposed to the entire gland, while still controversial, is gaining significant interest due to its potential to treat the disease with reduced complications. While the multi-focus nature of prostate cancer and the ability to identify regions of disease within the prostate remain critical challenges, multi-parametric MRI is showing promise in localizing cancer within the prostate by combining the information from quantitative T2, diffusion-weighted and dynamic contrast-enhanced imaging [Langer et al 2009]. Sensitive and specific prostate cancer diagnosis using MRI could be incorporated seamlessly in the treatment planning of MRI-guided transurethral ultrasound prostate therapy, without the need for image registration between the diagnostic, soft-tissue contrast and temperature feedback images. Additionally,
knowledge of the location of the cancer within the prostate relative to the ultrasound transducers within the urethra would make MRI-guided transurethral ultrasound therapy an ideal candidate for focal therapy [Eggener et al 2007]. All of the treatment delivery strategies developed in this thesis can be extended easily to focal therapy of the prostate, with similar or reduced thermal impact to the surrounding important structures. Furthermore, MRI-guided transurethral ultrasound therapy offers the targeting flexibility of heating conservatively the entire prostate gland to achieve an overall therapeutic effect, all the while generating more aggressive temperatures in the regions containing cancer. This treatment approach, which is a compromise between a radical and focal therapy, can be integrated within the active surveillance management of prostate cancer, potentially providing patients good disease control with minimal complications.

Finally, while the technology discussed in this thesis is being developed with the intention of being an alternative to conventional prostate cancer treatments, it can be applied to deliver controlled heating to a variety of other sites in the body accessible by intra-cavitary or interstitial devices and where MR thermometry can provide adequate temperature feedback.
6 References


Canadian Agency for Drugs and Technology in Health (2006) High-intensity Focused Ultrasound for Prostate Cancer. [http://www.cadth.ca.](http://www.cadth.ca.)


