Robotic HIFU for the Treatment of Prostate Cancer

Master of Engineering

Nanyang Technological University

Submitted by

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Abstract

The surgical world is experiencing a revolution brought about by the proliferation of minimally invasive technologies. The application of laparoscopic and endoscopic methods have extensively reduced the degree of invasiveness. With the rapid advances in computer and information science, a further challenge is the use of robotics and computer systems with suitable surgical procedures to create a fully integrated non-invasive treatment.

The work embodied in this thesis involves the design of a robotic system for the specific purpose of destroying prostate cancer endeavours to specify a low-cost clinic-based treatment modality that is easy to use and portable. Consequently, the three objectives of this project are; (a) to study the feasibility of delivery HIFU via the transperineal route; (b) to study the effectiveness of a selected HIFU transducer namely Imasonic, France; and (c) to devise a robotic manipulator to deliver HIFU to treat prostate cancer.

The HIFU treatment method can only be effective if the small focal region is accurately swept throughout the entire volume of tumour. This can be achieved by a mechanical scanned means. The position information of the treatment site can be achieved using a diagnostic ultrasound system. This project involves the conceptual design and development of such a robotic manipulator using ultrasound as a means of locating the prostate. Magnetic Resonance Spectroscopic (MRS) intervention with cross registration to ultrasound images is proposed to locate and destroy tumours more effectively.

Work has also been undertaken to investigate the characteristic of the HIFU transducer (customized fabricate from Imasonic, France). The temperature elevations along the HIFU beam path have been measured. The results show the temperature at focal region is relative high whereas other areas remained low. It showed the non-invasive nature of which cancer was destroyed at the focal region without damaging the surrounding healthy tissue.

The present work intends to initiate research into a robotic HIFU surgery system for the ablation of prostate cancer. The ultimate goal of this project is to provide a clinically proven non-invasive treatment modality for prostate cancer.
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INTRODUCTION AND PROJECT FORMULATION

1.1 Introduction

Cancer is one of the dire medical conditions that affect today's society. The factors that trigger this unnatural growth of cells are very poorly understood; and this lack of knowledge adversely impacts on the development of suitable curative therapies. Even the detection of cancers proves to be a difficult task. The surest way of detecting cancers is to obtain a biopsy sample of the tissue in question. Pathological tests are performed on these samples to determine if they are cancerous or not. Many a time, the biopsy samples are not retrieved from the actual cancer sites. In this case, the patient may be told he/she does not have cancer even if he/she is suffering from the disease, this complicating the matter further.

Cancer is described as a neoplasm† growth where the excess production of cells results mainly from:-

- Uncontrolled division of cells (in most cases); or
- Abnormally long lifetime of cells.

The growth can be benign (grows slowly without invasion and retains characteristics of the mature, differentiated tissue) or malignant (grows rapidly and destructively and is composed of atypical tissue). Prostate cancer occurs when malignant cells develop and form a tumour in the prostate gland. Localized prostate cancer is defined as a cancer

† Neoplasm: any new and abnormal growth; specifically a new growth of tissue in which the growth is uncontrolled and progressive.
confined within the prostate gland. In most cases, the cancer will grow slowly. However, it can grow quickly and spread to nearby lymph nodes. Lymph nodes are small, pea-sized pieces of tissue that filter and clean lymph, a clear liquid waste product. If prostate cancer has spreaded to lymph nodes when it is diagnosed, it means that there is higher chance that it has also spreaded to other parts of the body. Treatment of the cancer becomes more difficult when this happens.

Cancer of the prostate is the second leading cause of cancer death among men. It is primarily a disease of aging. Men in their 30's and 40's rarely develop prostate cancer, but the incidence increases steadily after 55 years of age. Approximately 80% of all cases occur in men over the age of 65, and by the age of eighty, 80% of all men have prostate cancer to some degree [Go Symmetry, 2002].

The world population was estimated to be 6.2 billion in mid-2002 as indicated by the Population Reference Bureau (PRB) [PRB, 2002]. This reflects an increase of more than 80 million over the previous 12 months, in which the elderly population demonstrated the largest increase at 2.4 percent. By 2025, the global over-65 population is projected to increase to 800 million – reaching 10 percent of the world population [WHO, 1998].

The average global life expectancy was 48 years in 1955; improved to 65 years in 1995 and is expected to reach 73 years in 2025 [WHO, 1998]. This trend clearly shows the increase in life expectancy over the years. Current demographic changes are also creating an unprecedented increasing proportion of the global elderly population.

The ministry of Health (Singapore) and Department of Statistics (Singapore) revealed that Singapore’s population reached 4.02 million in 2000 [State Health, 2000]. Generally, the population grew an average by about 1.9 percent annually. The aging trend in Singapore continued, with the number of elderly aged 65 years and above increasing to 237, 000 and comprising 7.3 percent of the total resident population.

Life expectancy in Singapore for the male gender was 68 years in 1980 and improved to 74 years in 1990 and 78 years in 2000. In 1998, WHO categorized Singapore into a group of nations possessing the second highest life expectancy (at 81 years) in the world [WHO,
Chapter 1: Introduction and Project Formulation

1998]. As such, this clearly showed that the Singapore population is expected to live a longer life.

As life expectancy continues to improve and coupled with the increase of an aging population, diseases that are common among elderly people would become more prevalent as time passes. With regards to the male gender, prostate cancer would be a main concern for the practicing physician as the number of men in need of treatment for prostate cancer is expected to rise, and with it the evaluation and treatment expenditure.

1.2 Statement of the Problems

Radiotherapy, systemic chemotherapy and radical surgery have long been the most effective treatment for cancer. However, localized prostate cancer is not responsive to either radiotherapy or chemotherapy. Radical surgery is the only curative approach for a very small number of patients.

Although there is active research into other forms of treatment for prostate cancer, (See Section 2.4) much of this research is concentrated in the West. These treatment modalities, which are developed around First World resources (large capital investment, health care services with good intensive care, latest medical tools e.g. CT, MR scanners), are totally beyond the reach of the poorer countries. Hence, the problem facing most developing countries is in finding a treatment for localized prostate cancer that is effective, easy to administer and cost-effective to be extensively implemented.

Another perspective to consider is the dilemma faced by the national health services of many developed countries. These services are under tremendous pressure to provide prompt health care to an ever-increasing population. However, most hospitals have long waiting lists with a number of people succumbing to their illnesses without being given proper treatment. There are many factors that relate to this predicament; one possible reason being that treatment is hampered by the disproportionately high number of procedures that depend on a few high cost systems e.g. MR and CT scanners, specialist
intensive care units, etc. There is now urgent research into the modification of treatment plans and research into new procedures that do not rely on the availability (or to minimize the use) of these expensive machines.

A possible solution to these problems can be formulated as follows:

Develop a prostate cancer treatment modality that is:

- **Low cost**  
  To be affordable to general hospitals of developing countries.

- **Reliant on readily available equipment**  
  Minimise the investment in associated equipment and tools, work within the resources of developing countries, alleviate the need for expensive machines in developed countries; thus helping to ease the financial burden on the national health services.

- **Clinic/Office based**  
  A treatment modality that does not depend on large centre, and the associated cost of pre- and post-operative care.

- **Portable**  
  Able to be moved between clinics, rather than being stationed permanently at one place. This facilitates greater access to rural regions, where health-care is very limited. Portability will also reduce the investment in a large number of machines.

- **Easy to use**  
  Computer-based protocol, with a rigorous monitoring routine, that will operate with minimum clinician input, and easy to use (and to learn).

- **Safe**  
  All the above must be achieved without compromising treatment efficacy and patient safety.
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1.3 Solution Proposal

Nanyang Technological University has a long track record for the development of computer-based technologies to assist in surgery [Phee et al., 1997; Phee et al., 1998; Lim et al., 2000; Ho et al., 2001]. More recently, there has been preliminary research in the use of high intensity focused ultrasound (HIFU) as a minimally or non-invasive surgical tool in breast cancer surgery [Chauhan et al., 2002]. To fulfil the requirement of an out-patient based treatment, the modality has to be totally non-invasive (most minimally invasive ('key-hole') procedures require a small incision that can only be safely done in a fully equipped operating room, and the patient would normally require a short stay in hospital). HIFU has the potential to provide non-invasive means of destroying deep-seated tissue without the need of general anaesthesia or postoperative care. Also extracorporeal HIFU is classified as a 'trackless' surgical modality, implying that the healthy tissue between the transducer and the treatment site is not damaged. It is only in the focal region of the beam that the temperature is sufficiently high to destroy tissue.

However, as the knowledge of the author, HIFU as a treatment modality for localized prostate cancer is still in its infancy. A number of research centres are currently conducting clinical trials to test the efficacy of this technique; with most reporting positive results from their experiments [Cheng et al., 1997; ter Haar, 1995]. The long term goal is to develop a portable, clinic based system to treat prostate cancer without the need for hospital stay. To fulfil such a goal, there may be a need for transfer of preoperative magnetic resonance (MR) images (which may be helpful to locate the cancer sites) from large MRI centres to the clinics.

1.3.1 Ultrasound

Ultrasound is a well-established imaging modality in the areas of medicine, biology and engineering. Its ease of application, low cost and radiation free operation make it the medical imaging modality of choice in most soft tissue diagnostic investigations. Recently, there has been renewed interest in HIFU as a surgical tool. Various types and configurations of transducers are currently being researched that would provide the safe
ablation of deep-seated tissue. The extracorporeal type of transducer (plane, bowl or array) provides the non-invasive modality for the trackless ablation of deep-seated tumour tissue.

The transducer needs to be positioned so that its focal point is on-target. The size of this focal point, however, is small when compared to the size of a large prostate tumour (about 2 cm in diameter). Hence, for this treatment modality to be effective, the focal point will need to be moved throughout the region of the prostate tumour. The accurate scanning of the focal point can only be achieved by computer-based mechanical means. A robotic manipulator will be ideally suited for this function. Further development could include a non-invasive temperature sensing system that could sense the temperature rise at the focal point. Such a system could be incorporated into the robot to form a closed-loop system which can ascertain the correct delivery of the HIFU energy. However, this development is beyond the scope of this thesis.

**1.3.2 Robotic Manipulator**

A robotic manipulator needs to be developed to secure and manipulate the HIFU transducer such that its effective work volume encapsulates the maximum size of treatable prostate tumour. The manipulator should be small, of a lightweight construction (meeting the requirement of portability) and have a small work envelop (a safety feature, which is typical of medical robots). The issues of safety must be central to the development of the manipulator.

One of the corner stones of developing a robotic system for surgery, is the issue of registration; i.e. informing the robot as to the relative position of the treatment site. Hence, the robotic manipulator under investigation must incorporate some method of registration.

Another important issue that needs to be borne in mind is that the transducers cannot be used in direct contact with the skin (unlike diagnostic transducers), nor can they be used in air. Hence, a couplant medium in the form of a large flexible water bag must be included in the design of the manipulator. This places further constraints on the design of the manipulator, in that all the electrical and electronic components need to be isolated from any contact with water.
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1.4 Project Objectives

In relation to using a robot to deliver HIFU for the treatment of prostate cancer, the project objectives can be stated as follows:

- To study the feasibility of delivering HIFU via the transperineal route.
- To study the effectiveness of a selected HIFU transducer namely Imasonic, France.
- To devise a robotic manipulator to deliver HIFU to treat prostate cancer.

Hence, the title of this thesis is a summation of the above:

Robotic HIFU for the Treatment of Prostate Cancer

The HIFU calibration and the development of the robotic system are considered as two separate and independent tasks. The technology of HIFU is still at its infant stage. Much advancement in this technology is expected in the near future. Thus, even if HIFU were to be considered inappropriate to be used to treat prostate cancer at this present time, it cannot be ruled out as a therapeutic alternative in the future as technology in this area improves. This justifies the parallel development of the robotic system which functions as a manipulator to position a therapeutic tool.

1.5 Scope

In the feasibility study of delivering HIFU via transperineal route, the parameters of the HIFU transducer will first be determined. These parameters include focal length and active diameter of the transducer. Frequency of the transducer is dependent of these two parameters and is a determining factor i.e. varying the intensity of the HIFU beam. The selections of the parameters are based on the Visible Human Project (VHP) data set. The focal length is chosen based on the anatomical geometry estimation of the distance between intervention tissues whereas the active diameter is estimated based on the VHP...
data set. The largest possible active diameter is chosen so that the HIFU beam can penetrate into the prostate without hitting the pelvic bone.

The transperineal route was chosen as it shows some advantages compared to other routes (see section 3.4). The size of transducer will be determined based on the mechanism used to scan or focus at the area of interest in the prostate. The transrectal ultrasound (TRUS) probe is used to detect cancerous tissue location in the prostate as an input for the positioning of HIFU transducer. The distance from the perineal wall to the prostate varies with patients. The proposed robot is to be designed accordingly to cater to patients of all builds. The HIFU beam used passes through the different tissues layer. Diffraction and deflection may occur. Experiments will be carried out to verify that sufficient intensity can be achieved for the chosen frequency after tissues attenuation. A Spherical Bowl HIFU transducer with fixed focal length will be used. The transducer will be procured from Imasonic, France.

If cancerous tissue is detected in the ultrasound images, it is very important to know the exact position of this cancerous tissue in the prostate with respect to the robot. The HIFU transducer can only be focused at the targeted point if the relation between ultrasound image coordinate with respect to robot is known. That relation will be obtained by using transrectal ultrasound probe. Transverse images will be used as they show the precise position in the axial axis of the probe.

The aforementioned studies establish the necessary specifications for a robotic HIFU system to be designed. In the designing of the robotic system, the aim is to position the HIFU transducer to focus at a desired location in the prostate under ultrasound image guidance. The robotic system consists of mechanisms that provide the necessary degrees of freedom for both the HIFU transducer and TRUS probe. A motorized system enables the HIFU transducer and TRUS probe to achieve the desired position for treatment. A supporting gantry/manipulator that moves the HIFU transducer and TRUS probe to a desired position with respect to the patient is required in the design. Consequently, three modules will be designed for the proposed robot, they are the Firing Positioner module (for therapy), Imaging module (for localization) and Manipulator module (for positioning).
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HIFU calibration will be carried out to ensure that the focused point temperature can be elevated to 60–80°C. At this range of temperature, the protein in the tissue denaturalized and probably causes cell death (see section 2.4.4). The temperature distribution along the beam path is investigated. It is to measure the degree of non-invasiveness or how the intervening and overlying tissue, other than the focused point is heated. The heat generated from the HIFU beam path must not cause extensive damage to the healthy tissue. The above test is limited to gelatine specimen as, unlike meat, it exhibits constant mechanical properties. After this HIFU calibration, the transducer will have to undergo in vitro tests. Two (2) tests are proposed, one to measure temperature rise to ensure enough heat is created to cause cell death. The other is to investigate its lesion after firing of HIFU at that particular area.

1.6 Thesis Organization

Chapter 2 gives an overview of the medical issues of prostate cancer. The anatomy and physiology of the prostate will be described. Prostate cancer will be discussed which includes the diagnosis, grading and staging and current treatment options. Finally, this chapter describes how thermotherapy, the use of elevated temperatures for the treatment of human malignancies, may be applied for various treatment modalities.

Chapter 3 introduces the usage of ultrasound technology in medicine. The biological effects of ultrasound will also be discussed. The formulation of this project, transperineal treatment, is derived by comparing the pros and cons of other existing routes.

Chapter 4 reviews the state-of-the-art of image guidance and robots in surgery. A number of registration techniques will be discussed at the end of this chapter.

Chapter 5 discusses present manipulator-based HIFU systems. The basic mechanisms of the proposed transperineal HIFU robot will be described. Localization of prostate cancer is achieved by transrectal ultrasound imaging. There are three modules in the proposed robot system viz. firing positioner module, imaging module and manipulator module. The
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design concepts and the considerations of these modules are discussed in detail. A surgical
protocol is also proposed at the end of the chapter.

Chapter 6 presents the material and methodology of the HIFU calibration. The experiment
scope is in various aspects which include temperature rise at focal point, temperature
distribution and in vitro test. The results will be presented together with the discussion.

Chapter 7 concludes the above work and presents the future work.
Chapter 2

MEDICAL ISSUES OF PROSTATE CANCER

2.1 Anatomy and Physiology of the Prostate

The three most common types of prostate disease are Benign Prostatic Hyperplasia (BPH), prostatitis, and prostate cancer. This chapter will briefly discuss the anatomy and physiology of the prostate, a wide range of prostate cancer treatment modalities and finally conclude with a number of specific thermotherapy procedures currently under investigation.

The prostate is a walnut-sized gland located in front of the rectum and just below the bladder. It wraps around a tube called the urethra that carries urine from the bladder out through the tip of the penis.

Figure 2-1: The male reproductive system.

(Adapted from [Mosby, 1994])
Prostate gland is part of the male reproductive system (Figure 2-1). Its main function is to produce a milky fluid (semen), which energizes the sperm and makes the vaginal canal less acidic. During the male orgasm, muscular contractions squeeze the prostate's fluid into the urethra to mix with the sperm that are propelled into the urethra from the testicles. This mixture then leaves the penis during ejaculation [Spence et al., 1987].

As a heterogeneous gland, the prostate is composed of glandular and fibromuscular tissues [Spence et al., 1987; Fornage, 1988]. It is cone-shaped, tapering from the base to apex, and oriented slightly obliquely downward and forwards. Its base adjoins the bladder neck whilst its apex merges with the membranous urethra to rest on the urogenital diaphragm.

The urethra traverses the prostate by entering near the middle of its base and exits the gland on its anterior surface above and in front of its apical portion. The ejaculatory ducts enter the base on its posterior aspect and run in an oblique fashion to emerge and terminate adjacent to the seminal colliculus. The junction between the prostatic urethra and ejaculatory duct is termed verumontanum and is an important anatomical landmark. Distal to the verumontanum is the sphincter mechanism, which holds or releases urine outflow.

The prostate is divided into three areas (Figure 2-2) - the peripheral zone, the transition zone, and the central zone - with a layer of tissue surrounding all three [Christopher, 2002].
Chapter 2: Medical Issues of Prostate Cancer

The peripheral zone, which wraps like a horseshoe around the posterior and lateral portions of the gland, contains 70 percent of the glandular tissue and is the site of the majority (almost 80 percent) of prostate adenocarcinomas. Prostate adenocarcinoma is the clinical term for cancer that begins as a tumour on the prostate gland. This zone is the region most susceptible to clinically significant inflammation.

The transition zone, which lies anterior to the central zone and surrounds the distal internal urethral sphincter, is the site of origin of the majority of hyperplastic nodules and of almost 15 percent of prostate adenocarcinomas.

The central zone includes the region through which the ejaculatory ducts pass on their way to the urethra. Only a small percentage of adenocarcinomas are thought to arise from this region of the gland.

2.2 Detecting of Prostate Cancer

There are no clear symptoms of prostate cancer that can be easily assessed by the patient himself. This makes prostate cancer very different from breast cancer or testicular cancer in which regular self examination can be important in finding early signs of the disease. A big problem with prostate cancer is that many of the early signs of the disease can be caused by other disorders or, worse still, are just among the normal consequences of growing older. Another big problem is that usually prostate cancer does not give signs or symptoms for many years after the disease starts to develop. Early prostate cancer may have no symptoms and can only be found with regular prostate check-ups by doctor. These tests can often detect, or help rule out, prostate cancer.

Diagnosing prostate cancer is a multi-step process usually consisting of one, or more, of the following evaluations:

- DRE (Digital Rectal Examinations): During the procedure, the doctor inserts a lubricated gloved finger into the rectum. Because the prostate is located in front of the
rectum, the doctor can feel it to determine the size, shape and consistency of the prostate. If the prostate is enlarged but feels soft and palpable, the patient is likely to have BPH. If the prostate is hard or nodular, the patient would be asked to undergo further testing to rule out prostate cancer. However, only posterior part of the prostate can be directly felt by the finger.

- **PSA (Prostate Specific Antigen):** PSA, or prostate-specific-antigen, is a protein produced only by the prostate tissue. Very high levels of PSA usually indicate prostate cancer, but moderately elevated levels may indicate either cancer or BPH. PSA is secreted by the epithelial cells of the prostate gland including cancer cells; an elevated level in the blood indicates an abnormal condition of the prostate gland, either benign or malignant; it is used to detect potential problems in the prostate gland and to follow the progress of prostate cancer therapy. It is now the most often used prognostic markers for progression of prostate cancer. More information can be found in [Richard, 1996].

Follow-up visits with doctor are extremely important if one has an unusual DRE, or if the PSA level is high. The doctor may order more tests or suggest repeating the PSA tests.

If the DRE or PSA are unusual, the doctor may repeat the tests or request an ultrasound and other procedures. These evaluation tools may include:

- **TransRectal UltraSound (TRUS).**
- Imaging procedures, such as computerized tomography (CT) scans, MRI scans, or others.
- **Biopsy.**

The diagnosis of cancer is confirmed only by a biopsy -- the removal of a small tissue sample for microscopic examination.

### 2.3 Grading and Staging of Prostate Cancer

Another step in the diagnostic process is grading the cancer cells, which is a measurement of how aggressive the tumour is. Grading is done in the laboratory with cells taken from
the prostate gland during biopsy. The cancer cells are measured by how closely they look like normal cells.

According to the National Cancer Institute, one way of grading prostate cancer is the Gleason system. This grading system is based on a number range from 2 to 10. The lower the number, the lower the grade, and the slower the cancer is growing. On the other hand, the higher the score, the higher the grade of the tumour. High-grade tumours grow more quickly than low-grade tumours, and are more likely to spread to other parts of the body. Grades under 4 mean that the cancer cells look similar to your normal cells, and the cancer is likely to be less aggressive. Grades 5 to 7 are in the intermediate range. This means that the cancer cells do not look like normal cells, and are more likely to be aggressive and grow faster. Grades 8 to 10 indicate that the cancer cells are more likely to be very aggressive in growth.

If cancer is found in the prostate, the stage, or extent, of the disease should be known. Staging is an attempt to determine whether the cancer has spread and, if so, what areas of the body are affected. Various blood and imaging tests are used to determine the stage of the disease. Treatment decisions depend on these findings.

In general, the different systems attempt to classify stage of the cancer are as follows:

- To evaluate the size and location of the tumour.
- To evaluate whether the cancer cells have moved beyond the tumour, but are still within a specific area or organ of the body.
- To evaluate whether the cancer cells have spread beyond the specific area or organ of the body to other tissues beyond it.
- To evaluate whether the cancer cells have spreaded into the lymph nodes.
- To evaluate whether the cancer cells have metastasised into another part of the body.

Results from staging and grading the cancer provide information a cancer team can use to define a treatment plan that will be presented to and discussed with the patient and family members.
Prostate staging can be described by using T (tumour size), N (extent of spread to lymph nodes), and M (extent of spread to other parts of the body). The TNM (Tumour, Nodes, Metastases) Classification of prostatic cancer, which is proposed by the International Union Against Cancer, is generally accepted in the clinical staging of the tumour where

\[
\begin{align*}
T_0 &= \text{No evidence of primary tumour.} \\
T_1 &= \text{Tumour not palpable or visible by imaging but could be found incidentally on histology of specimen of resected prostate tissue after some procedure done on the prostate.} \\
T_2 &= \text{Tumour seen on imaging or palpable on DRE but the tumour has not invaded the prostatic capsule or involved the seminal vesicles.} \\
T_3 &= \text{Tumour has involved the seminal vesicles or has invaded the prostatic capsule.} \\
T_4 &= \text{Tumour has invaded other surrounding structures other than the seminal vesicles e.g. bladder neck, rectum, pelvic floor muscles or pelvis wall.} \\
N_0 &= \text{No lymph node involvement.} \\
N_1 &= \text{Involvement of regional lymph nodes, e.g. pelvic lymph nodes.} \\
M_0 &= \text{No distant metastases.} \\
M_1 &= \text{Distant metastases.}
\end{align*}
\]

Tumours with a stage up to T2N0M0 are classified as organ confined tumours and have a better prognosis. Once the tumour invades the prostate capsule or there is nodal involvement or distant metastases, the prognosis becomes poor. Staging is important in assessing the degree to which the tumour has spread and to predict the prognosis.

Alternatively, a four-staged, Roman numeral classification is often used. The stages in this system reflect the extensiveness of the cancer, with Stage I being the least extensive and Stage IV being the most extensive. Colon cancer uses a "Duke's" classification with the earliest stage term "Duke's A" and the most advanced being a "Duke's D". Using these forms of staging does not preclude also categorizing cancer in the TMN classification. Table 2-1 compares the cancerous staging standard and its equivalence.
Chapter 2: Medical Issues of Prostate Cancer

### Stage I

**TNM**

- **T1**
- **N0**
- **M0**

**Duke’s A**

### Stage II

**TNM**

- **T2**
- **N0**
- **M0**

**Duke’s B**

### Stage III

**TNM**

- **T3**
- **N0**
- **M0**

**Duke’s C**

### Stage IV

**TNM**

- **T4**
- **N0**
- **M0**

**Duke’s D**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>TNM</th>
<th>GROUP</th>
<th>GROUP</th>
<th>DUKE’S</th>
</tr>
</thead>
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<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>Duke’s A</td>
</tr>
<tr>
<td>Stage I</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Duke’s B</td>
</tr>
<tr>
<td>Stage II</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>any T</td>
<td>N1</td>
<td>M0</td>
<td>Duke’s C</td>
</tr>
<tr>
<td>Stage III</td>
<td>any T</td>
<td>N2, N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>any T</td>
<td>any N</td>
<td>M1 (distant)</td>
<td>Duke’s D</td>
</tr>
</tbody>
</table>

Table 2-1: The equivalent of the cancerous staging standard.

### 2.4 Current Treatment Options

The treatment that is prescribed for prostate cancer should take into account the followings:

- general health
- age
- expected life span
- personal preferences
- anticipated effects of the treatment
- stage and grade of the cancer

Generally, prostate cancer is a progressive disease that is likely to grow and spread over a period of time, unless it is treated.

Research and clinical trials are continuously underway searching for new treatments for prostate cancer. Currently, the most common treatment options include:

- Radical Prostatectomy
  - Radical Retropubic Prostatectomy
  - Nerve-Sparing Radical Prostatectomy
  - Radical Perineal Prostatectomy
  - Laparoscopic Radical Prostatectomy
Chapter 2: Medical Issues of Prostate Cancer

- Radiation Therapy
  - External Beam Radiation Therapy (EBRT)
  - Brachytherapy
- Watchful waiting
- Hormone therapy
- Chemotherapy
- Cryosurgery

The above mentioned treatment options can be divided into three categories of treatment namely open surgery, minimal invasive surgery and non-invasive surgery. Radical Prostatectomy is an open surgery which requires opening on the patient body (Laparoscopic Radical Prostatectomy is a minimal invasive surgery). Minimal invasive surgery requires small opening holes on the patient body and the treatment includes brachytherapy, hormone therapy and cryosurgery. External beam radiation therapy is a non-invasive treatment which does not require any opening on the patient. However, external beam radiation therapy will damage the intervention tissue during operation.

The main treatment options for early stage prostatic carcinoma are radical prostatectomy, external beam radiotherapy and interstitial brachytherapy. Careful observation without immediate active treatment is also an option, especially for patients of advanced age and those with concurrent disease. Radical prostatectomy, in which the entire prostate gland is removed, is the most common treatment and is considered as the “Gold standard”.

Treatment options for early-stage prostate cancer include:
Radical prostatectomy: surgery to remove the prostate gland and surrounding tissue and structures.
Radiation therapy: use of high-energy, external x-ray beams or internal radiation seeds to destroy cancerous tissue.
Watchful waiting: observation and monitoring of PSA levels with no immediate active treatment.
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Treatment options for advanced prostate cancer include:

**Hormone therapy:** use of drugs to inhibit the action or block the production of male hormones that cause prostate cancer to grow. Hormone therapy may include surgical removal of the testicles, which produce the male hormone testosterone.

**Radiation therapy:** use of high-energy, external x-ray beams to destroy cancerous tissue. A combination of hormone and radiation therapies

**Chemotherapy:** use of toxic drugs to destroy cancer cells.

A more detailed medical review of these treatments, especially the most common therapies for early-stage prostate cancer treatment (cancer is localized), which include radical prostatectomy and radiation therapy, will be presented in the following sections.

### 2.4.1 Radical prostatectomy

Radical prostatectomy has been recommended by some for almost all stages of prostate cancer. It is widely used only in men who are likely to afford the cure (well to do man). In general, this applies to men with stages T1 and T2 disease with low-to-moderate grade pathology and a life expectancy of more than 10 years. In this method the prostate and some of the tissue around it are removed, usually through an incision in the lower abdomen. The advantage of this option is a one-time procedure that may cure the early stage of prostate cancer.

There are four common methods of radical therapy (i.e., removal of the whole prostate) namely radical retropubic prostatectomy, nerve-sparing radical prostatectomy, radical perineal prostatectomy and laparoscopic radical prostatectomy.

**Radical retropubic prostatectomy**

In this procedure, the surgeon cuts down through the abdomen in order to expose the patient's prostate. In a complex set of procedures, the surgeon then cuts out as much of the prostate as he or she possibly can. Ideally, the entire prostate is removed together with the seminal vesicles. After removal of the prostate and the seminal vesicles, the urethra is carefully rejoined to the "neck" of the bladder so that on recovery the patient will be able
to urinate in a normal fashion after a relatively short period of time (usually a few weeks or months).

Nerve-sparing radical prostatectomy
The nerve-sparing technique is a modified form of radical retropubic prostatectomy. The bundles of nerves on either side of the prostate gland are responsible for erections. If they appear to be cancer-free, they are not removed with the entire prostate gland. If the nerves are not damaged during surgery, men have a better chance of having erections again between two and 18 months after the operation.

Radical perineal prostatectomy
In this procedure, the surgeon cuts up through the perineum in order to expose the patient's prostate. While the different surgical route requires significant technical differences in the manner in which the operation is carried out, the surgical principles are pretty much the same as for a radical retropubic prostatectomy. The complications are fewer than that of radical retropubic prostatectomy but they still exist.

Laparoscopic radical prostatectomy
Laparoscopic radical prostatectomy is a new technique in which a laparoscope, a slim tube with a tiny video camera on the end, is inserted into a small incision in the abdomen. While watching the procedure on a TV monitor, the surgeon inserts instruments through another small incision and removes the prostate gland.

This minimally invasive procedure is a promising alternative to the standard, "open" prostate surgery, with reduced blood loss, postoperative pain, catheterization time and hospital stay. The technique of laparoscopic nerve-sparing prostatectomy to preserve potency is still evolving.

Whether laparoscopic radical prostatectomy will gain worldwide acceptance is unknown. To date, no in-depth clinical studies have been conducted to compare the long-term benefits of the laparoscopic technique to standard techniques. This approach will likely be limited in the United States in the near future; given the time it takes to master the complexities of the procedure and the relatively few urologists performing it.
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A retrospective study of 955 men with localized prostate cancer [Walsh et al., 1994], indicates that radical prostatectomy cures the majority of men with confined disease; after ten years, only four percent of patients have local recurrence, and seven percent have metastases. These results are similar to those found by Oelefein et al., who followed 238 men and found that the five-year disease-specific survival rate was 92 percent in patients with a Gleason score of 7, and 79 percent in patients with a Gleason score greater than 7 [Oelefein et al., 1995]. In this study, the Gleason score was the strongest predictor of disease progression and survival.

In a retrospective study of the incidence of complications after radical prostatectomy, 65 percent of patients developed impotence, and while only a small fraction become incontinent, 60 percent reported the need for pads or clamps for urinary wetness [Fowler et al., 1993].

Radical prostatectomy requires hospitalization, and it is not tolerated by patients who are not in good health. Furthermore, there is morbidity associated with general anaesthesia and major surgery. Oefelein et al., reported that the major cause of death after retropubic radical prostatectomy is prostate cancer, not competing causes [Oelefein et al., 1997]. This led these investigators to study the surgical procedure; they concluded that surgery itself may dislodge cancerous cells from the prostate, leading to local recurrence.

2.4.2 Radiation therapy

Radiation therapy is the use of high-energy beams or particles to kill cancer cells or make them unable to grow and divide. The goal is to do maximise harm to the tumour while doing minimal harm to adjacent normal tissue. Unlike cancer cells, most normal cells can repair the damage caused by radiation.

External beam radiation therapy

High incidences of impotence and incontinence, low tolerance for surgery among aged patients, and disease recurrence have generated interest in alternatives to radical prostatectomy. Foremost among these is External Beam Radiation Therapy (EBRT).
In principle, external beam radiation therapy uses a system for the delivery of high-powered radiation to the prostate and immediately surrounding parts of the anatomy.

In the first place, the radiation oncologist will carry out a simulation of the radiotherapy. The objective is to set up a system that will ensure the delivery of the most appropriate dose of radiation to a particular patient's prostate, depending upon the size and position of that prostate and its location relevant to other nearby organs. Various methods have been used in order to try to direct the radiation accurately to the prostate and to minimize extraneous radiation of surrounding tissues. Typical treatments have, until recently, used rectangular treatment fields. With the advent of multi-leaf collimation, irregularly shaped treatment fields are being used to reduce the radiation dose delivered to adjacent normal tissues. It is now possible to specify treatment plans so that the treatment volume conforms to the shape of the planning tumour volume. Such techniques (known as conformal radiotherapy) reduce the radiation dose delivered to normal tissue adjacent to the prostate, and permit increased radiation doses to be delivered to the tumour itself.

Actual treatment can begin shortly after the treatment planning is completed. A full course of external beam radiation usually takes about six or eight weeks with 10 to 15 minutes each day. By delivering the radiation for five days each week, the body is able to regain strength for two days each weekend.

The advantages of external beam radiation compared to surgery are as follows:
- There is no surgery and no anaesthesia, so there is lower morbidity and mortality.
- There is no risk from surgical bleeding and transfusion.
- The rate of impotence resulting from radiation therapy is generally less than that from surgery.
- Incontinence rates are generally low (at less than five percent).
- There is good long-term control of the cancer.

† The planning tumour volume is the volume of gross diseases plus (1) a margin to include likely sites of occult cells and (2) a margin to account for uncertainties in treatment delivery. The planning tumour volume is also known as the target volume. The treatment volume is the volume which receives the radiation absorbed dose prescribed in the treatment.
On the other end of the scale, there are some disadvantages:

- There is a 10-15 percent possibility of radiation damage to the bladder and/or the rectum.
- The rate of long-term impotence is about 30-50 percent.
- There is a rare occurrence of serious side effects such as radiation-induced cystitis, proctitis, and enteritis. These are usually reversible but may be chronic and can occasionally necessitate surgical intervention.
- Therapy takes 6-8 weeks compared to a few days.
- Side effects such as vomiting, nausea, stomach disorder etc.

Patients with locally confined prostate cancer, with no nodal involvement or metastases, are well served by EBRT. The ten-year outcome of such patients is equal to that obtained by radical prostatectomy in similar patients, without the operative mortality or incontinence that accompany radical prostatectomy [Hanks, 1994]. Pollack et al., have found that doses above 67 Gy (absorbed doses) reduce local failure in EBRT of early-stage cancer [Pollack et al., 1998]. Kaplan et al., have shown that EBRT is as effective in men under the age of sixty as it is for men over that age, and conclude that EBRT is a viable alternative to radical prostatectomy for younger men [Kaplan et al., 1994].

Hanks [Hanks, 1991], in a retrospective study of patients undergoing EBRT or radical prostatectomy, found that patients with cancers confined to a single lobe of the prostate had equal 15-year survival whether treated with external beam radiation therapy or radical prostatectomy. However, when both lobes are involved, patients treated with EBRT show superior survival and disease-free survival, compared to results with radical prostatectomy. A further advantage of EBRT is the low incidence of complication. In a study of 289 patients with confined cancer who received EBRT, only mild and moderate complications were observed in 13 percent of patients [Greskovich et al., 1991]. Similar results were found by Beard et al., who retrospectively studied 441 patients who had undergone EBRT [Beard et al., 1998]. While 39 percent of patients had rectal complications and 33 percent had bladder complications, only 14 percent of patients required treatment. Impotence occurred in 62 percent of patients after treatment.
Disadvantages of radiation therapy for prostate cancer include significant morbidity (bladder and bowel injury), a high incidence of persistent disease, development of subsequent primary prostatic carcinomas, and anxiety due to the delayed time for evaluation of treatment outcome [Kirby et al., 1996]. EBRT can be inconvenient for the patient, as a typical treatment can consist of up to thirty fractions delivered over six to eight weeks. Day-to-day organ motion and variations in daily patient positioning also hamper the effectiveness of EBRT. The effects of treatment volume motion and morbidity from bladder and bowel injury can be reduced with another radiation therapy, which is brachytherapy.

Larger treatment volumes increase radio-toxicity in normal tissues; hence, there is interest in applying conformal EBRT to prostatic carcinoma. As the treatment volume increases, there is an increase in the rate of genitourinary complications for men receiving EBRT [Vijayakumar et al., 1993]. In a study of conformal EBRT, Hanks et al., used PSA levels to identify patients with "biochemically no evidence of disease" (bEND) [Hanks et al., 1997]. They found that conformal three-dimensional EBRT of localized prostate cancer produced 5-year bEND results that are comparable to results obtained with nerve-sparing prostatectomy. Early results showed a modest decrease in the disease-free rate at five years. However, the incidence of incontinence and impotence was not reported. From these results, it can be extrapolated that promising results could be expected with highly conformal brachytherapy treatments.

**Brachytherapy**

Brachytherapy is a form of radiation therapy in which physicians implants radioactive pellets or seeds into the prostate gland in order to kill prostate cancer cells. The term “brachytherapy” was coined by Forsell in 1931. It is derived from the Greek word brachio, meaning short, and refers to “treatment with a radioisotope at a short distance”. This method is also called “Radioactive Seed Implantation” or “Internal Radiation Therapy” [Hilaris et al., 1996].

Most radiation treatments are delivered with teletherapy, in which the source of radiation is distant form the target; in brachytherapy, the source is placed in or near the target. Because the radioactive sources used in Brachytherapy deposit the entire absorbed dose
within a few millimetres of the source, the sources can be arranged so that the radiation dose delivered to adjacent normal tissues is minimized, and the dose delivered to the target volume itself is maximized.

External beam radiation therapy produces survival rates that are at least equal to those observed with radical prostatectomy, with complication rates generally reduced compared to radical prostatectomy. The incidence of complications is further reduced by conformal radiotherapy, indicating the advantage of conformal treatment volumes. Brachytherapy provides intrinsically conformal radiotherapy for two reasons: (1) there is no irradiation of normal tissue between the patient's surface and the treatment volume; (2), by optimizing the seed placement, the treatment volume can be made to closely approximate the target volume; and (3), high radiation dose density can be given. The short treatment times involved for both temporary and permanent implants make this treatment especially attractive for active patients.

Early brachytherapy treatments involving manual placement of the seeds, which exposed the practitioner to high radiation doses, have been superseded by after-loading techniques, in which a hollow needle or applicator is placed in the target. The radioactive source is then positioned through this channel. The occupational exposures encountered in this manual after-loading have been further reduced with the introduction of remote after-loading, which uses a mechanical device to load the source by remote control. Remote after-loading, which uses sources of high activity, has allowed the introduction of high dose rate and pulsed dose rate brachytherapy, which would otherwise give prohibitively large radiation doses to hospital personnel.

Although the use of radium to treat prostate cancer was reported in 1913, interest in brachytherapy remained low due to the radiation exposure to operating room staff. The introduction of megavoltage linear accelerators in the early 1960s, capable of producing improved teletherapy dose distributions slowed the development of brachytherapy. Shortly thereafter, however, the development of after-loading techniques renewed interest in brachytherapy. By the mid-1980s, a number of radioactive implantation procedures for prostate carcinoma appeared in the literature.
Retropubic implantation of radioactive seeds to the prostate, which produced poor dose uniformity, has been replaced by transperineal implantation because of the development of transrectal ultrasound (TRUS). Transperineal implants can be used alone or in combination with EBRT in the treatment of prostate cancer. Complication rates with brachytherapy are minimal, and are more likely to occur in patients who have undergone transurethral resection of the prostate (TURP). Otherwise, patients who undergo transperineal implantation show excellent quality of life [Arterbery et al., 1997].

2.4.3 Other therapies

Watchful Waiting [Feeney, 1999]
There is currently no treatment available that has been proven capable of providing a cure, capable of extending life, or of no postoperative complications. In addition, all treatments have undesirable side effects that can seriously detract the patient's quality of life for the rest of his days. Therefore, watchful waiting is recommended for patients of advanced age and those with concurrent disease.

Slow progressing tumours can often be left alone, especially in the elderly, because the risk of death from the cancer is less than from other diseases. However, the tumour must be monitored at regular intervals and watched closely. Many men are unwilling to go this route and unable to live with the idea that there is a cancer growing inside them.

In the watchful waiting approach, the patient and his physician agree upon what is to be watched (PSA, DRE, TRUS, etc.) and what is being waited for (development of numerical values of parameters being watched, progression to symptoms, etc.), with the intention of taking the next step after the occurrence of that event.

Hormone therapy
Hormone therapy is most commonly used to treat cancer that has spread (metastasized) outside the pelvic area (Stages N+ and M+). Two types of hormone therapy can be used:

† It is important to note that ultrasound images cannot be used to detect cancer locations but is reliable enough to help determine the location and shape of the prostate.
(1) surgical removal of the testicles that produce male hormones, or (2) drugs that prevent
the production or block the action of testosterone and other male hormones. Hormone
therapy cannot cure prostate cancer. Instead, it slows the cancer's growth and reduces the
size of the tumour or tumours.

Hormone therapy in combination with radiation therapy or surgery is also used in
advanced stages of cancer when the disease has spread locally beyond the prostate (Stages
T3-T4). This therapy helps extend life and relieve symptoms. When the cancer has spread
beyond the prostate, complete surgical removal of the prostate is not common. In patients
with early-stage cancer (Stage T2), hormone therapy may be used in combination with
radiation therapy. A short course of hormone therapy can also be used prior to surgery to
reduce the size of the prostate and make it easier to remove.

The primary strategy of hormone therapy is to decrease the production of testosterone by
the testicles. Regardless of the method of hormone therapy, however, the decrease in
testosterone can result in certain side effects. These commonly include hot flashes, a loss
of sexual desire, and impotence.

Chemotherapy
A number of factors complicate the decision to use cytotoxic chemotherapy in men with
advanced prostate cancer. Among these factors are complicating illnesses which may
occur in this population of older men, reduced functional capabilities which may occur in
men with advanced prostate cancer and the long-standing belief that "chemotherapy" has
no role in the management of prostate cancer.

Cryosurgery
Cryosurgery (also called Cryotherapy) of the prostate, like brachytherapy, is a technique
for treating prostate cancer without the trauma of major or open surgery. Minimal blood
loss, little discomfort, and a single day in the hospital are the advantages of this approach.

The basic concept behind cryosurgery is that the surgeon can use extreme cold to freeze
the prostate, which causes the cells to break down as they are first frozen and then thawed.
The treatment involves the placement of five needles into the prostate through the perineal
skin while the patient is under anaesthesia. The needles are placed with guidance from a transrectal ultrasound probe. Through each needle, a guide wire is placed and the needle removed. Over the guide wire, a slim plastic straw (a sheath) is placed through which a narrow (3 mm) metal cryoprobe is introduced into the prostate. Liquid nitrogen is then pumped into each of the cryoprobes. The end of each probe gets extremely cold and the entire prostate can be frozen.

Traditionally, the urethra is protected with a urethral warming catheter, however, in doing so, the prostate near the warmer is also protected and some cancers will not be cured. However, there are new approaches allowing complete destruction of the urethra with total destruction of the prostate and all the cancer. These new treatments have resulted in 100 percent cures to date in patients with PSA levels under 10 and better than 80 percent cures (0.0 PSA levels) in patients with PSA levels up to about 40 as reported by Gould (1999).

However, cryosurgery is not a widely accepted procedure for the treatment of prostate cancer at the current time. Many experts consider this technique to be experimental due to the lack of long-term follow-up data.

The known side effects of cryosurgery can include impotence (in about 80 percent of patients), scarring of the urethra and urinary dysfunction (which are relatively unusual), and irritation of the bladder, the urethra, the rectal wall, and the genitalia. This last group of side effects can include pain on urination, a burning sensation during urination, frequent and unexpected urination, blood in the urine (hematuria), and swelling of the penis or the scrotum.

### 2.4.4 Thermotherapy

The use of elevated temperatures for the treatment of human malignancies is as ancient as medicine itself. Eclipsed by the spectacular progress of radiotherapy and chemotherapy for more than half a century, thermotherapy is again the subject of a great deal of enthusiasm for its use in cancer treatment. In comparison to other modern therapies, thermotherapy is considered cheaper, faster, less invasive and just as (or at times more) effective. There are
various means in which the body can be heated. These methods depend on the treatment modality being applied (Table 2-2).

<table>
<thead>
<tr>
<th>LOCALIZED HEATING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Invasive – External</td>
<td>Microwave applicators</td>
</tr>
<tr>
<td>RF applicators (Inductively or capacitively coupled)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound applicators</td>
<td></td>
</tr>
<tr>
<td>Invasive - Interstitial and Intercavitary</td>
<td>Microwave antenna (helical and dipole)</td>
</tr>
<tr>
<td>RF localised current field electrodes</td>
<td></td>
</tr>
<tr>
<td>Ferromagnetic seeds heated by magnetic induction</td>
<td></td>
</tr>
<tr>
<td>Ultrasound transducers</td>
<td></td>
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<tr>
<td>Resistive wire</td>
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</tr>
<tr>
<td>Fibre-optic coupled laser</td>
<td></td>
</tr>
<tr>
<td>laser-induced interstitial thermotherapy (LITT)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REGIONAL HEATING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>External</td>
<td>Similar to above with larger elements</td>
</tr>
<tr>
<td>Invasive</td>
<td>Local</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHOLE BODY HEATING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>External</td>
<td>Electric blankets, hot water/wax tubs, radiant heating</td>
</tr>
<tr>
<td>Invasive</td>
<td>Perfusion with heated blood</td>
</tr>
</tbody>
</table>

Table 2-2: Methods of heating Tissue.
(Adapted from [Sullivan et al., 1997])

There are intensive studies being conducted for effective minimally invasive thermo therapies. The following discusses some of the most important modalities currently being studied for the destruction of cancer by heating (or cooling).

Cryosurgery (see section 2.4.3)
Cryosurgery (also called cryotherapy) is the use of extreme cold to destroy cancer cells. Traditionally, it has been used to treat superficial tumours, but with the recent advances in probe technology, physicians have begun using it as a treatment for internal tumours. Surgeons use ultrasound to guide a probe (cryoprobe) through the prostate gland to the tumour. Liquid nitrogen is circulated through the probe, which chills the probe tip to
-196°C. The probe, which is placed in contact with the tumour, kills the tumour by freezing [Fiefel et al., 1998].

Radiofrequency therapy
Radiofrequency (RF) energy, which has been used successfully for almost 40 years in the neurosurgical field to produce small intracerebral lesions, has proved to be a safe, well-controlled and reproducible source of energy. The method works by heating and destroying tissue within a specific volume around an electrode, which emits RF-energy. This energy translates to ion agitation, which is converted into heat, inducing cellular death by coagulation necrosis. US, CT and fluoroscopy have been the image guidance techniques employed for this percutaneous interventional procedure. With recent advance in electrode tip technology and MR compatible materials, various studies are being conducted with MR as the guidance tool [Trubenbach et al., 1998].

Laser Surgery
Laser (Nd:YAG) -induced interstitial thermotherapy (LITT) has become a clinical tool for treating various malignancies e.g. tumours in liver, brain, ENT, or abdominal locations, as well as for treating benign alterations, e.g. prostate adenomas (BPH) and vascular malfunction. Bare fibre or diffusing applicators are punctured into the pathological volume to distribute the laser energy within the region of interest. With near-red lasers, photon absorption and heat conduction will obtain coagulative and hyperthermic effects. Higher power levels are now available with new internally cooled laser systems [Fuchs et al., 1998; Russ et al., 1998].

Microwave therapy
Percutaneous microwave coagulation therapy (PMCT) is a new therapeutic technique for the treatment of solid neoplasms [Sakaguchi et al., 1998]. The microwave electrode is inserted into the prostate gland via urethral (transurethral). The microwaves emitted from the electrode, heat the tissue by molecular vibration, resulting in thermal coagulation in the target area. The basic mechanism for heat generation consists of changing the polarities of water molecules in the tissue. The polarised molecules follow the induction of the electrical field of the microwave. As the electrical field is altered at ultra-high speeds (2450 MHz), microwaves are produced which generate heat. The heat is not directed from
external sources but generated in the tissue itself, and this may be the greatest difference between this and other forms of interstitial thermotherapy (but similar to Focused Ultrasound). The coagulated area is elliptic, with ±2 cm maximal diameter and 1 cm minimal diameter at the tip of the electrode.

The Dutch Hyperthermia Group has published good results from a multi-centre study of the combination of radiotherapy and hyperthermia for the control of advancing cervical tumours. They placed a number of extracorporeal electromagnetic antennae around the treatment site to raise the local temperature to 40 –50° C [van der Zee et al., 2000].

**Focused Ultrasound therapy**

High intensity ultrasound can be focused within tissue to produce trackless lesions, i.e. to destroy selected tissue volumes without damage to structures lying between the source of the sound beam (the transducer) and the target volume [Malcolm et al., 1996]. HIFU has only recently become a practical for treating deep-seated tumours. High intensity beams can readily be achieved using either bowl or lens focusing procedures and, by choice of a suitable acoustic frequency, regions of tissue destruction can be induced at the selected depth in the body. The primary mechanism of damage is thermal, i.e. ‘cooking’ of the tissues. The lesions have a spatially sharp demarcation between regions of normal and dead cells. The technique is suitable for the treatment of any tissue that can be readily visualised using diagnostic ultrasound, providing an adequate acoustic window can be achieved between the skin and the target tissue.
Chapter 3

ULTRASOUND IN MEDICINE

3.1 Introduction

Ultrasound is well established as a non-invasive, non-traumatic, safe imaging tool. Although the quality of the ultrasonic image and resultant interpretation and diagnosis is very operator-dependent, it is still the widely used imaging modality of choice for soft tissue investigation.

Ultrasound is a form of mechanical energy that is unique amongst available medical radiation in that it can be sharply focused within tissue. This means that the regions of high energy within the ultrasound beam (the focal region) may be placed accurately within well-defined volumes. There is an increase in temperature in the focal region due to the biological effects that ultrasound has on the tissue. This allows the possibility of using an external source of ultrasound to heat deep-seated tissue within the body [ter Haar, 1989].

Comparatively, radio frequency (RF) waves have a low tissue absorption rate but a very long wavelength (in the order of metres). Microwaves and lasers have shorter wavelengths (cm to mm) but much higher tissue absorption rates. Although RF waves can be transmitted to locations well beneath the skin, they cannot be focused to a precise volume. High frequency microwaves and lasers can be focused to a precise volume but they cannot be transmitted through the skin and tissue without causing damage to them [Daum et al., 1999].

Recent research in high intensity focused ultrasound, as a hyperthermia modality, has shown promising results as an alternative or adjunct therapy in the fight against cancer [Sanghvi, 1996]. Due to the good penetration of ultrasound, it has the potential to produce
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therapeutic temperatures for either regional heating (hyperthermia) or small areas of high temperature for tissue destruction (focused ultrasound surgery). The intensity of the heat induced is dependent on a number of factors. These include type of biological tissue, transducer size (active diameter) and shape (focal length), frequency of the ultrasound, excitation power of the transducers, time intervals of exposure, etc. These factors must be carefully considered to provide the most effective temperature elevation and distributions, and the absence of unwanted heating.

A brief overview of the various heating modalities was given in Section 2.4.4. This section discusses in more detail, the use of HIFU in thermotherapy. The choice of treatment routes for the prostate using HIFU will be discussed. The selection of transducer parameters e.g. focal length, active diameter and frequency will also be presented.

3.2 Ultrasound in Cancer Therapy

The application of heat to aid in the healing of injuries is a remedy that has been handed down through the ages. As technology advanced, so did the method of inducing heat into the body. Ultrasound has been under investigation from early 20th century [Wood et al., 1927] as a modality for heating or destroying deep-seated tissue. It has since been researched as one of the few non-invasive modalities in the fight against cancer.

Focused ultrasound was first proposed by Lynn [Lynn et al., 1944] as a potential technique for neurosurgery. Despite considerable research in the next few decades, the use of focused ultrasound for neuro-surgery did not reach the clinic [Basauri et al., 1962; Fry, 1977; Warwick et al., 1968]. One of the reasons for this was the lack of precise technology of transducers and piezoelectric material which resulted in big transducers that required large access craniotomies.

Focused surgery requires the ultrasound beams to be sharply focused, and driven at high intensities to create the high temperatures necessary of tissue destruction. However, focused transducers can be used for the therapeutic heating to deep-seated tissue to help in
recuperation, particularly of soft tissue damaged through spots injuries. It was also found that the cyclic pressure waves of the acoustic beam acts as a micro-message which further benefits the healing process. More recently, research has shown that this regional heating (hyperthermia) has increased the efficacy of oncological drug treatment by aiding the diffusion of drugs into the tumour cells [Falk et al., 2001].

3.2.1 Focused Surgery

“A rationale for the ultrasonic ablation of a tumour mass as a potential cancer therapy involves reducing the total number of tumour cells in the mass to a level where the immune system might be capable of taking any remaining viable cells to extinction” [Fry et al., 1978]. Additionally, the immune system might be further activated due to the nature of ultrasonically destroyed cell residual in the tumour mass. It is also conceptually possible to destroy all the tumour cells so that no viable cells remain after an appropriate ultrasound irradiation. This hypothesis has been the subject of research for a number of years.

Fry [Fry et al., 1978; Gordon, 1967] further developed an early system of his, used for the treatment of Parkinson's disease, into a multiple probe system for the destruction of deep-seated cancer tissue in the brain. This method proved very invasive as it required a large vault of the skull to be removed to allow access to the ultrasound beams of the four transducers. Although some efforts have been carried out towards a non-invasive, trans-skull approach to the treatment site, these were not very promising. Following these poor results, researchers explored other applications for focused ultrasound, notable in urology and oncology.

Two commercially available systems have been developed for the transrectal treatment of BPH. The Sonablate™ device (Focus Surgery Inc. Indianapolis, IN USA) uses the same transducer for imaging and therapy [Madersbacher et al., 1994; Sanghvi, 1996]. A French system, Ablatherm™ (Technomed International, Lyon, France) uses two separate transducers for imaging and treatment [Chapelon et al., 1999]. Capabilities of both these systems are now being extended to treat prostate cancer.
Watkin et al., [Watkin et al., 1995] has discussed the urological applications of HIFU for BPH, prostatic, bladder and renal cancer. Their work established fundamental dosing predictions for treatment by HIFU.

MR guidance and thermal mapping has been explored by Hynynen et al., [Hynynen et al., 1993] from the possible treatment of breast cancer.

The mechanism of cell destruction by high intensity ultrasound will now be discussed.

### 3.3 High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU), as a surgical tool, is capable of selective and precise destruction of small volumes of diseased tissue by inducing temperatures of 60-80°C at a specific location within the organ of interest. This technique, also referred to as Focused Ultrasound Surgery (FUS), differs from hyperthermia mainly on the basis of dosage levels, intensity and exposure time. The temperature induced in the targeted tissue produces rapid, complete, irreversible damage. The exposure times are very small (1-10 sec) as compared to hyperthermia (30 - 60 min). Under these short exposure times, the problems posed by heat diffusion due to blood perfusion are, therefore less significant [Watkin et al., 1995].

FUS is unlike conventional surgery, in that there are no incisions or removal of diseased tissue. The high intensity ultrasound (generated from transducers) destroys, or denatures, the cells, which are broken down and eliminated by the body’s natural metabolic and excretion systems.

#### 3.3.1 Thermal Mechanism

The energy transported by an ultrasound beam is attenuated and scattered as it passes through any viscous medium. This energy is responsible for various reversible or irreversible biological changes depending upon the irradiation conditions. The amount of
heat generated is dependent on the characteristic of the ultrasound wave and the biological tissue that it passes through. The energy lost from the primary beam in travelling unit distance, \( dI/dx \), is given by \( \alpha I \). To obtain an estimate of the temperature rise that may occur in tissue due to the attenuation of an ultrasonic beam, let us assume that all the energy removed from the primary beam leads to local tissue heating, i.e. attenuation is entirely due to absorption. The rate of heat deposition per unit volume, \( \dot{Q} \), is given by

\[
\dot{Q} = \alpha I
\]

(Eq. 3-1)

If no heat is lost from this volume by conduction, convection or radiation,

\[
\dot{Q} = \rho c_m \frac{dT}{dt}
\]

(Eq. 3-2)

or

\[
\frac{dT}{dt} = \frac{\alpha I}{\rho c_m}
\]

(Eq. 3-3)

where
- \( I \) = Intensity at depth \( x \)
- \( \alpha \) = attenuation coefficient
- \( \rho \) = density (kgm\(^{-3}\))
- \( c_m \) = heat capacity of the medium, and
- \( \frac{dT}{dt} \) = rate of temperature rise.

### 3.3.2 Stress Mechanism

Ultrasound imposes mechanical pressure on irradiated biological tissues and fluids. The pressure varies spatially, as well as temporally, as the wave propagates in the medium. The pressure induces stress on the tissue, which could result in damage to the cell structure. The pressure and stress may also produce a phenomenon called ‘stasis’, in which the cell boundaries are held stationary while the plasma experiences a to and fro motion, which occurs as a result of build-up of radiation forces in a standing wave field. This
reciprocating motion could lead to high shear stresses within the cell that result in tissue destruction.

### 3.3.3 Cavitation

Acoustic cavitation is the formation and activity of gas- or vapour-filled cavities (bubbles) in a medium exposed to an ultrasonic field. Cavitation occurs in the presence of air or gas cavities in liquid suspension. There are two types of bubble activity, viz. stable cavitation and collapse (or transient) cavitation. Stable cavities oscillate in response to the ultrasonic pressure field. The bubble radius varies about an equilibrium value, and the cavity exits for a number of acoustic cycles. High shear stresses are often associated with this type of cavitation.

Collapse cavities oscillate in an unstable manner, grow to several times their equilibrium size, and collapse violently. This activity takes place over a few cycles of the sound field. It has been found that a remarkable increase in temperature (thousands of degrees Kelvin), pressure (of the order of several atmospheres) and chemical reactivity may occur at the collapse sites.

### 3.3.4 HIFU Transducer

Ultrasound is generated by an electrical device called a transducer, which converts electrical energy to high frequency acoustic waves (and vice versa). Most transducers used for medical diagnostic applications are used for both the generation of ultrasound (active mode) and the detection of ultrasound (passive mode) in the form of the reflected waves from a particular target. These medical ultrasound transducers are specially designed depending upon the application. The choice of construction material and electrical insulation are of vital importance in the specification of transducers [Fish, 1990; Gooberman, 1968; Wells, 1977].

There are three principle means by which ultrasound waves (energy) can be focused, viz. a bowl shaped active layer, a plane transducer with external focusing elements (e.g. lenses, shaped acoustic mirrors), or electronic phased arrays. The delicate alignment of the
acoustic mirrors and the high cost of manufacture and complex electronic circuitry of the array transducers have precluded these types of transducers from consideration for this project. Since establishing a particular HIFU probe is not a part of this project, a widely used and commercially available transducer type, the focal bowl, is procured for this work (Imasonic Inc.)

There are two broad groups of focused ultrasound surgery classified by the method of surgery involved and the type of transducer that is used [ter Haar, 1995].

3.3.5 Invasive method

The transducers for invasive therapy are small in size, usually unfocused and sit next to the treatment site so that all the energy can be directly transmitted. The transducers are normally inserted via catheterisation. These miniaturised transducers are called interstitial probes. A notable example is the transurethral catheters prototype developed by Seip et al., (2000) which contain multiple HIFU transducers at the tip.

3.3.6 Non-invasive method

In this approach, the acoustic energy is transmitted to the target site without the need for any access incisions. This group is further divided into two subgroups: -

- **Extracorporeal transducers**: These bowl-shaped transducers are used to treat/ablate tissues which can be approached through large acoustical windows on the skin, e.g. the treatment of tissues like liver, kidney, bladder, prostate etc, through the abdominal and/or perineal approaches.

- **Intra-cavitary transducers**: These are probe-shaped transducers, which are inserted into body cavities, to provide a shorter ultrasound path to the target tissue. Since the target tissue is approached from a smaller distance, the probes are smaller in aperture and can be tailored to a size and shape as suited to the cavity. The notable application in this context is the transrectal approach for the ablation of regions of prostate tissue. This transrectal route to the prostate has been exploited by a number of researchers,
with the resulting commercialisation of two HIFU systems, viz. Sonoblate\textsuperscript{TM} from Focus Surgery Inc. (Minneapolis, USA) and Ablatherm\textsuperscript{TM} from Technomed Inc. (France).

### 3.4 HIFU treatment route for prostate disease

There are four possible routes to treat prostate tumour using HIFU, viz. transrectal, transabdominal, transurethral and transperineal (Figure 3-1). The above routes can access prostate gland without hitting the bone at certain angulations.

![Possible HIFU treatment routes for prostate cancer.](image)

**Figure 3-1: Possible HIFU treatment routes for prostate cancer.**

In the transrectal route, the transducer is placed in the rectum and applies energy to the prostate through the rectal wall. Taking the transurethral route, the transducer is inserted through the urethral and applies energy to the prostate. In the transperineal route, the HIFU energy passes through the perineal wall to the prostate. Finally, in the transabdominal route, the HIFU energy goes through the abdominal wall and the urinary bladder before reaching the prostate.

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1993) and ter Haar, (2001) used transabdominal route for the prostate treatment. The transurethral route prostate treatment was used by Seip et al., (2000). Until now, to the knowledge of the author, no one has published a paper using HIFU via the transperineal route to treat prostate disease.

In this project, the transperineal route has been chosen as the preferred route to deliver the HIFU energy. The drawbacks of the other three routes, as compared to transperineal route, are as follows:

- Transrectal route:
  The workspace is small due to the limited space of rectum: - the HIFU can only destroy tissue within fixed focal length accessible from the rectum. In the treatment of prostate cancer, a range of transducer with different focal lengths is required to cover the cancerous area at different depths. The treatment is time consuming because of the need for changing different transducers with different focal lengths. In addition, the need for an entire range of transducers would increase the cost of the system (however, one must note that there is a costly alternative to alter the focal length electronically).

  Furthermore, small transducers (compared to transabdominal and transperineal routes) cost more as more expensive technologies are involved to build them. As the transrectal ultrasound (TRUS) probe is the preferred imaging means for treatment of the prostate, both transducer and probe must be inserted into the rectum. This further constrains the transducer design in terms of size and definitely increases the manufacturing cost (there is also the alternative of combining the imaging and therapeutic transducer as a single transducer). The transducer’s shape used for this route is round with cutting edges on both sides. This design aims to enlarge the transducer as much as possible but still allows insertion into the rectum. The transducer in such a design will cause the HIFU beam not to focus sharply at the target. Unlike treatment of BPH, which has a focal point of about 4 cm, prostate cancer normally begins in the peripheral zone which is very near to the rectal wall. As the focal point of transducer is small (1~3 cm), rectal wall burn may occur. A high quality cooling system would be required to cool down the rectal wall to avoid burning.
However, this would also increase the overall cost of the equipment. This cooling system may also cool down the focal point of the transducer which causes the targeted temperature to drop below the desired temperature. Another drawback is that the HIFU beam may be reflected on the thick wall and the transducer [Marberger et al., 1994]. Commercial devices, using phased array transducer for treatment of prostate cancer, are also currently being investigated [Curiel et al., 2002; Tan et al., 2000]. The phased array transducer is costly, difficult to manufacture etc. At this point of time, both commercial devices (Sonablate™ and Ablatherm™) have not yet been approved by the FDA (Food and Drug Administration).

- Transabdominal route:
  The transabdominal route for the treatment of prostate diseases using HIFU is the longest route among the four available routes. By surveying the human anatomy, part of the accessibility to the prostate gland is obstructed by the pelvic bone. This prevents the prostate gland from being treated using HIFU. Breathing movements will also cause the tissue along the beam path to move making it a difficult target. Furthermore, it is very difficult to incorporate the transrectal ultrasound probe to the transabdominal transducer because both instruments are very far apart.

- Transurethral route:
  The drawbacks are similar to the transrectal route. Since the workspace is very small, the smallest among four routes, a robotic system to drive the transducer cannot be applied here. Furthermore, it would cause trauma on the urethral.

On the other hand, the transperineal route using HIFU for the prostate cancer treatment has many advantages. Even though the workspace is not the largest; it facilitates the incorporation of a robotic system for HIFU treatment. An effective scan of the prostate using HIFU can be obtained. Although part of the prostate gland is obstructed by the pelvic bone via the HIFU transperineal route, it can be focused at the peripheral zone of the prostate where more than 80 percent of the prostate cancer begins. The perineal wall and focus point is not too near, thus avoiding the problem of wall heating. The surrounding tissue remains stationary all the time as breathing does not affect this route. The transrectal ultrasound imaging system can be incorporated easily using a robotic
system as the physical location is near. With the above considerations, the transperineal route was chosen.

With knowledge of high intensity focused ultrasound, the specifications for the non-invasive, extracorporeal transducers for the destruction of prostate tumour cells, via the transperineal route will now be formulated.

### 3.5 Transducer parameters estimation

There are two main HIFU transducer parameters that must be estimated in order to select a focal bowl type transducer. These parameters include focal length and active diameter. Frequency is dependent of these two parameters and is a determining factor i.e. varying the intensity of the HIFU beam. The Visible Human Project (VHP) data set is used for the estimation of these parameters. The objective of using data from the VHP is to obtain a rough guide to the human anatomical layout. Knowledge of the position of the pelvic bone and the relative position of the prostate is important in selection of a particular transducer and designing a robotic system. With such data, one can then cater for the degree of freedoms (DOFs) required to manipulate the HIFU efficiently and effectively. The current work shows some considerations using only a specific anatomy. In the future, when the entire system were to be commercialised, one can then consider about whether a one-size-fits-all system or robots of various sizes are to be realized to cater for patients of all builds. After the estimation of the parameters, the transducer is designed accordingly to fit in the proposed HIFU robot. The transducer is constructed by a commercial vendor (Imasonic Inc., France).

#### 3.5.1 Focal length estimation

This parameter of the transducer is primarily determined on the anatomical location of the prostate in the transperineal route. For this estimation, the anatomical data extracted from Visible Human Project (VHP) was used. In the transperineal treatment route, the HIFU
beam will pass through the perineal wall, fat, muscle before reaching the prostate. The thickness of the respective intervention tissue layers are shown in Figure 3-2.

![Figure 3-2: Tissue layer from the perineal wall to the prostate.](Data extracted from Visible Human Project)

The distance from the perineal wall to the prostate gland (bladder neck) is about 94 mm. Therefore, a focal length of 130 mm was selected, with some allowance for a degassed water medium.

### 3.5.2 Active diameter estimation

The active diameter is estimated based on the anatomical geometry study. In order to obtain a rough guide to the human anatomical layout, the knowledge of the positions of the pelvic bone and the prostate gland is very important. Therefore, the 3D model for pelvic bone and prostate gland, which is extracted from the VHP data set, is developed in CAD format (see Appendix A). In CAD format, the dimensions are shown to scale. Similarly, for realism, the size of the proposed HIFU beam is drawn to the actual size of the beam.
Due to the fact that the HIFU beam may be obstructed by the pelvic bone on the way to the prostate, rotation about the transducer mechanism is required to produce the minimum window for beam penetration. Therefore, the maximum possible active diameter can be obtained. A greater active diameter is required to induce higher intensity of the transducer.

A series of trial and error tests is used to determine the active diameter of transducer. The HIFU beam path is inserted into the 3D model in a location with the focal point at the bladder neck of the prostate. Then, the beam path rotates about the transducer to cover the peripheral zone of the prostate. Once the beam path hits the pelvic bone, the active diameter is reduced until the beam path avoids the pelvic bone. It was found that an active diameter of 54 mm was the maximum size that can be used without hitting the pelvic bone.

Figure 3-3: Study of anatomical geometry.

The coronal, transverse and sagittal views for the location of prostate gland and HIFU transducer (to scale) are shown in Figure 3-3. The HIFU transducer can be rotated about its centre like a ball joint.

From the coronal view, if the HIFU beam is rotated about the transducer centre, a deviation of $\pm 6^\circ$ (as shown) is able to cover a fairly good area of the prostate. Since almost 80 percent of prostate cancers begin in the peripheral zone, and only T1/2M0N0 grade (early stage) is of interest, the peripheral zone is targeted.
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The highest possibility for the HIFU beam to “hit” the pelvic bone are at areas A or B (as illustrated in Figure 3-4) with the maximum deflection of 6° and focused at the deepest area. Since the pelvic bone is quite symmetrical about the mid-sagittal plane, only one of these two areas (area A is considered in this case) is considered for this simulation. By rotating the 3D model (not shown here), with the simulated beam path, the HIFU beam is not obstructed by the pelvic bone at area A. Thus, it can be concluded that with the transducer’s active diameter of 54 mm, the HIFU beam can avoid “hitting” the pelvic bone to reach the prostate treatment area.

![Figure 3-4: 3D model simulation (in correct proportion).](image)

3.5.3 Frequency estimation

From Huygen’s wave propagation principle, the magnitude of the acoustic pressure at a given point in the field of an ultrasound beam can be evaluated by the complex summation of pressure amplitudes from individual Huygen’s point sources at the transducer face. The effect that the variation of the frequency on the pressure distribution in an ultrasound field can be evaluated. This project adapts an algorithm based on the cylindrical wave equation for the calculation of acoustic pressure amplitude and intensity distribution of compression waves from an earlier work. It assumes axially-symmetric calculations for the field distributions. The wave equation used is [Porges, 1979; Davies et al., 1998]:

\[
p(r, t) = A \frac{2 \lambda}{nr} e^{i(\omega t - kr)}
\]

(Eq. 3-4)
where \( p(r,t) \) is the elemental acoustic pressure component at a distance \( r \) from the transducer at time \( t \). \( A \) is an arbitrary constant, \( \lambda \) is the wavelength of acoustic waves, \( i \) is the imaginary component of the expression, \( \omega \) is the angular frequency, and \( k \) is the wave number.

**Figure 3-5: The geometry for the calculation of the pressure field \( p(r,\theta,t) \) at an observer point \( O \).**

The algorithm (Eq.3-4) for the pressure amplitude was adapted for the evaluation of axial intensity distributions in order to study the dependence of the geometry of the focal region on the frequency at the selected active diameter of the transducer. Figure 3-6 illustrates this relationship which aids in the selection of the frequency of operation for this application.
As seen from Figure 3-6, increase in frequency results in higher intensity and shows more concentrated focal regions with increasing frequencies.

It has been reported that the spatial average intensity required for prostate tissue is 1680 W/cm$^2$ [Madersbacher et al., 1994]. The electro-acoustic efficiency of the transducer is about 50 percent, hence the peak intensity of 3360 W/cm$^2$ (1680/0.5) is deduced. Referring to Figure 3-6, frequency of 1.7 MHz is therefore selected.

With the results of this study, a Spherical Bowl HIFU Transducer with frequency of 1.7 MHz and active diameter of 54 mm with focal length of 130 mm was procured (Imasonic Inc., France). The selection of parameters of transducer is considered a preliminary one. Experiments will need to be carried out to verify the selection parameters (see Chapter 6).
Chapter 4

IMAGE GUIDANCE AND ROBOTS IN SURGERY

4.1 Introduction

Computers in medicine have long since evolved from being a huge and efficient filing system of the sixties and seventies to being integrated in every aspect of health care of the eighties and nineties. Apart from the computer-based systems used in administration and in patient monitoring and care, computers have become the complex driving engines of medical robotics, diagnostic systems, imaging systems and critical care systems.

This chapter will provide a brief overview of the use of computers in medical imaging systems and medical robotics systems. The next section focuses on medical imaging systems, with particular interest in the imaging of the prostate.

4.2 An Overview of Computer Based Medical Imaging Techniques

The precise location and continued knowledge of the treatment area is one of the most important aspects of medical robotics and computer assisted surgery. The robotic system has to be “shown” the exact position of the treatment area. The anatomical location of the tumours is found following diagnostic analysis of physiological and pathological ailments. Imaging modalities will normally confirm the presence and location of unusual masses.

The following section provides an overview of the modalities that can be used in the imaging of the prostate. Included in this discussion will be information on their applicability of the imaging technique as a registration tool, its ease of use and its cost.
This will provide a framework for choosing the imaging system that would be used as the registration tool of the envisaged robotic treatment modality under development.

### 4.2.1 X-ray Imaging

X-rays, part of the electromagnetic spectrum with a short wave length, have the ability to penetrate materials that do not transmit visible light. They pass relatively unimpeded through materials of low density and low atomic weight, but are stopped by substances of high densities (hence the ability of lead to provide protection from the harmful X-rays). When X-ray photons hit a phosphor screen, light is emitted, which can be detected by photographic film or amplified, by an image intensifier, to produce a visible image in real time (fluoroscopy). Gas, fat, soft tissue and water can be differentiated on a radiograph due to differences in density. Bones (calcium), having a high atomic weight, absorbs much of the radiation, producing a clear white image on the radiograph.

X-ray imaging can only be carried out in specially constructed facilities, which provide containment for the harmful radiation. Medical personnel working within this facility must don cumbersome lead-lined suits. Another major disadvantage is that the radiation is harmful in the human body i.e. the body can safely withstand a very short exposure to X-rays. Therefore X-ray imaging is rarely used for lengthy registration procedures.

The Computer Tomography (CT) method of forming images from X-rays was developed and introduced into clinical use by a British physicist, Godfrey Hounsfield, in 1972. In CT (sometimes referred to as CAT - Computerised Axial Tomography), the X-ray tube is rotated around the patient and the x-ray beam impinges on an array of detectors as it emerges from the patient. The intensity at each angle is recorded. By a computer technique involving the solution of many simultaneous equations, a two-dimensional image is produced of an axial slice (7-10 mm) through the patient. By packing these slices together a composite image can be formed. This computer image can then be rotated and viewed from any angle.
4.2.2 Ultrasound (US)

When high-frequency sound waves pass through soft tissue, echoes are produced at interfaces (changes in the tissue type and tissue density) and the depth of the source of the echo can be calculated from the time lapsed between the production of the sound and its detection (speed of sound in soft tissue being used in the calculations). When an ultrasound beam is scanned through an arc, combining the direction of the beam with the depth of the echo, a cross sectional 2D image of the internal organ can be obtained. Modern ultrasound machines permit rapid scanning, resulting in ‘real-time’ images.

However, the information from a single 2D image is far from enough to describe a 3D prostate gland. A surgeon usually moves the 2D-scanning plane of the ultrasound probe forward and backward to get an overall understanding of the whole gland [Richard et al., 1993]. Alternatively, a motorized stepper drives the probe of a conventional 2D ultrasound scanner and captures a stack of parallel 2D images, which can be converted to 3D image data (Figure 4-1).

![Series of Ultrasound Images](image1)

![Outlined Curves](image2)

**Figure 4-1: Conversion of a series of ultrasound images to 3D image data.**

(Adapted from [Wu et al., 2001])

4.2.3 Magnetic resonance imaging (MRI)

This principle is based on the fact that some nuclei (those with unpaired electrons) behave like tiny magnets. Hydrogen nuclei (protons) are particularly suitable since they are normally present in vast numbers in the body tissues. These protons align themselves when exposed to a strong magnetic field. The fields used in clinical practice range from
0.15 to 1.5 Tesla (1500 to 15 000 Gauss) as compared with the earth’s magnetic field of 0.5 Gauss. The alignment of these protons is displaced when exposed to a radio-wave of a certain frequency. They return to their alignment immediately after the pulse ceases, releasing radio wave energy which are detected by receiver coils. The computational analysis of these signals gives rise to the image. The intensity and duration of the signal emitted depends on the density of hydrogen nuclei and the degree to which they are bound in the tissue. Differences in these parameters provide soft tissue contrast. If MRI images stack in series, a 3D-model computer generated volume of the prostate can be obtained (Figure 4-2).

![Series of MRI Images](image1.png) ![3D reconstructed surface](image2.png)

**Figure 4-2: Convert the series of MRI images to 3D image data.**

(Adapted from [Wu et al., 2001])

### 4.2.4 Magnetic resonance spectroscopic (MRS)

Magnetic Resonance Spectroscopic (MRS) is an imaging technique based on cellular metabolism, with which it is possible to determine the content of various metabolites in the prostate such as citrate, choline and creatine. MRS is a software enhancement of MRI which reveals a chemical map on an MRI image. In doing so, the most probable cancer sites can be predetermined. Prostate cancer is characterized by a decreased level of citrate and an increased level of choline [Marinetter et al., 1999]. Cancer diagnostic is only possible if the ratio of choline plus creatine to citrate exceeds 2 above population norms or as definite if that ratio exceeds 3 standard deviations above the norm. MRS images provide even better detection and localization of prostate cancer than MRI images, with
the spatial resolution up to 0.24 cm$^3$ which corresponds to a cubic volume of 6 mm length [Scheidler et al., 1999].

From the MRI/MRS images, the locations of the prostate cancer can be obtained pre-operatively. By stacking the images series, a computer generated surface of the prostate can be obtained showing the locations of the cancer. This surface can be matched with the intra-operative transrectal ultrasound surface of the prostate obtained from the same patient (Figure 4-3). The resulting matched surface shows the positions of the prostate cancer with respect to the ultrasound probe. This information can be used by the robotic system. Therefore, the images guidance provide more accurate and requires less skill from practitioner. With such cross registration between pre-operative MRI/MRS, the prostate surface and cancer locations can be identified quickly and intra-operation ultrasound in the operating table.

Figure 4-3: The corresponding cancerous location in ultrasound and MRI images.
4.3 An overview of Robotic Systems in Medicine

Figure 4-4 illustrates the levels of man/machine interaction.

![Hierarchy of Man/Machine Relationship](Adapted from [Thring, 1983])

The shape of the figure is representative of the degree of physical human involvement; i.e. at the lowest level there is maximum physical human involvement in the task and at the highest level there is minimal physical human involvement [Thring, 1983]. This illustration will now be described in terms of medical/surgical applications.

At the lowest level, Level 1, it is the simple machine in which man provides the power as well as the controlling skill. The tool can be regarded as an extension of the surgeon’s body, since he grasps it firmly and guides its motion directly with his own muscular effort e.g.
- administering an injection with a needle and syringe;
- making an incision with a scalpel;
- the shaping of bone with saws and files, etc.

Level 2 is the powered machine or tool. The power most often comes from pneumatics, hydraulics or electricity. Here man is fully responsible for controlling the system e.g.
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- operating a powered saw or drill;
- performing surgery with a laser knife;
- tissue resection using a diathermy.

Level 3 is simple automation. These are the machines, which are powered and carry out complex programs for which man instructs them; e.g.
- the digital computer, which is capable of very quick and complex mathematical operations for pre-operative planning, imaging and guidance;
- ventilators, heart/lung and kidney machines.

Level 4 is the man-extenders. These are powered systems that operate as extensions to the human operator; providing him with the ability to work in hostile environments, with super-human strength and in some cases with greater dexterity and manoeuvrability. However, they only carry out tasks when man is connected to them in “real time”, e.g.
- tele-manipulators, which enable the skill of a human operator to be exercised remotely from his body; and
- powered artificial limbs controlled by the action of other muscles of the disabled person.

Level 5 is the robot systems, which are powered and programmed and will continue to undertake a task with very little or no supervision. The robot system may include a variety of sensing functions and may have limited capability of decision making. Presently, there is no medical robotic system that has been developed that works totally autonomously. Safety, ethical and legal issues prevent the robot from being readily accepted into the operating room.

Humans and machines have complementary strengths and limitations and the overall goal is to find ways to use them together to provide better and more cost-effective care than can be provided by either alone [Preising et al., 1991]. Recognised advantages of robotic systems include:

- The ability to accurately position and reposition surgical tools.
- The ability to apply precisely calibrated forces.
- The potential for reduction in tremor as compared to human hands.
The ability to scale the magnitude of forces and motions to be either larger or smaller than those that are possible by humans.

The ability to provide a stable platform for supporting and positioning surgical sensors, cameras, or instruments in a tireless manner.

The beginning of the last decade brought with it a dramatic increase in the usage of robots outside the automobile, appliance and hazardous materials industries. A significant contributing factor to this increased use is the robot’s ability to dynamically interact with its environment in a precise manner. However, the acceptance of robots in health care has been slowed by safety concerns [Davies, 1993]. Intimate interaction between robotic systems and patients in a medical environment is potentially dangerous because most industrial robots are controlled in an open manner and would not detect or predict collisions with the environment, patient, or medical attendants. This means that robots for use in surgery are to be custom designed and built. These systems would be required to react to given situations, by comparison of actual behaviour with referenced characteristic behaviour of the medium, during operations [DiGioia et al., 1996]. The robot device is expected to provide the accuracy and precision of positioning of the surgical tools but dependent on the surgeon for the treatment planning, critical decision making and final cutting of tissue.

Ever since the first International Advanced Robotics Programme (IARP) conference in 1988 at which Patrick Finlay plotted out the course of Medical Robotics and Computer Assisted Surgery [Finlay, 1988], there has been strong collaboration between surgeons, engineers and computer scientists in developing numerous applications for robots in medicine. In the early years, industrial robots were simply modified for medical applications [Kelly et al., 1988; Lavallee et al., 1996]. However, questions regarding the safety and legal liability soon led researchers to develop specific robots for specific applications [Davies, 1993].

Recently there has been a mushrooming of robotic applications in medicine, following remarkable advances in high quality imaging and the development of sensitive force and tactile sensors [Webb, 1988; Mansfield et al., 1982]. These applications have been
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approached from many directions, [Lavallee et al., 1996] and can be classified into a number of specific research areas:-

4.3.1 Computer Assisted Surgery – CAS

The main difference between the terms 'robotic' and 'computer assisted' surgery is that robots are motorised system somehow; whilst computer assisted systems are generally manually either powered by the surgeon [Davies, 2000] or backdriven [Harris et al., 1998]. At the core of the CAS system is a 3D image of the treatment site and an effective tracking system. There are two types of tracking systems:-

- **Optical based tracking and navigation systems.** These systems involve markers (e.g. LED's, IREDs (infrared emitting diodes) reflectors) mounted on the surgical tools and a set of cameras. The cameras measure the positions of the markers on the tool and the distances are triangulated to determine its position in 3D space (Figure 4-5). This kind of system is expensive, especially when many cameras are required to track a large field of view in order to achieve a desired resolution. Furthermore, this system can be problematic. The line of vision between the sensors and the cameras must not be obscured by the surgeon or other theatre staff, as this will result in a breakdown in the tracking procedure. A notable example of these systems is the Philip’s EasyGuide Surgical Navigation System.

![Figure 4-5: Image guided surgery.](Adapted from [Bale et al., 2001])
In Fig. 4-5, the treatment site is pre-operatively scanned with the reference fixture (1). The surgeon uses a tool (2), which has IREDs embedded in it, to plan the best possible approach to the target. The position of the tool is monitored by the cameras (3) which 'see' the IRED's. The computer system overlays the position of the tool on the pre-operative scans of the patient. These images are displayed on the monitor (4).

**Passive manipulator arm tracking systems.** These systems use a robotic arm to assist the surgeon to precisely align instruments. The position and orientation of the tool/fixture can be determined from the analysis of the joint displacements of the manipulator. The disadvantage of this system is that the manipulator arms can be cumbersome and restrict the surgeon in the free motion of the attached tools. The use of the manipulator, however, can help damp out unwanted hand tremor, and with the addition of electromagnetic brakes, can be used to lock fixtures in place while the surgeon continues the operation manually.

### 4.3.2 Surgical Robots

A surgical robot is *'a powered computer controlled manipulator with artificial sensing that can be reprogrammed to move and position tools to carry out a range of surgical tasks'* [Davies, 2000]. Such robots should not replace the surgeon, but should 'assist' the surgeon while under his/her supervision. Surgical Robots can be divided into two classes; passive (power-off) mode or active mode (to perform surgery under tight control/supervision).

#### 4.3.2.1 Passive Surgical Robots

These are powered robots used as passive holding fixtures for intra-operative guidance and tool orientation with respect to the surgical target. This is achieved either by sensor based optical tracking systems or passive manipulator arm tracking systems, in which a robot arm is use to assist the surgeon aligning the instruments precisely, relative to the patient. One of the earliest positioning/orienting robots was developed at Grenoble University Hospital for use in neurosurgery [Lavallee et al., 1996]. A standard industrial robot was modified for use in an operating theatre. The patient's head is held in a frame, which is attached prior to scanning. The robot, after registering itself to the head frame, can
accurately position a guide through which the surgeon can insert biopsy needles into the patient (Figure 4-6). Similar work was carried out by Kwoh et al., in 1985 [Kwoh et al., 1988]. More recent is the special purpose robot developed by Innovative Medical Machines International, (IMMI, Lyon, France) for neurosurgery (Figure 4-7).

The Surgical Robotics Laboratory (SRL) at the Department for Maxillofacial Surgery Plastic and Reconstructive Surgery at the Humboldt University, Berlin; have embarked on an ambitious project to integrate a number of different systems for computer assisted surgery. The special equipment comprises two robots, a navigation system, mobile CT scanner and immense computing power. The complete integrated system is reported to operate as a Robot Assisted Guidance System for implanting rigid catheters; for tools such as electric drills, tapers, screwdrivers, electric saws etc.; as a positioning and fixing system for bones, implants, transplants and as a holding system for retractor hooks etc. (Figure 4-8).

Figure 4-6: Image guided operating robot – Grenoble.

(Adapted from [Taylor et al., 1995])
Figure 4-7: “NeuroMate” developed by IMMI.

(Adapted from [Neuromate, 2002])

Figure 4-8: Totally integrated CAS system developed at SRL.

(Adapted from [Lueth et al., 1998])

The system comprises a mobile CT scanner (A), overhead guidance, monitoring and imaging passive arms (B) and floor mounted modified industrial robots (C).
4.3.2.2 Active Robots

Active surgery robots are powered-on systems that can perform actual surgical manoeuvres automatically, under the close supervision and control of the surgeon. They have the potential of performing more complex motions than the passive robots or, in many instances, the surgeon. However, safety concerns are great, and for this reason most active robots have been developed specifically for the task.

Robotic surgery was pioneered by Prof. B.L. Davies at Imperial College, London, where a special purpose, fully active robot for human prostatectomies was developed [Davies et al., 1991]. On the basis of transrectal ultrasound, the PROBOT (prostate robot) automatically undertook a partial resection of the prostate for the treatment of BPH. At Nanyang Technological University, Singapore, another group of researchers developed another version of PROBOT known as URObot (Figure 4-9). The URObot system was designed as a universal platform that can accommodate several urological procedures including electrosurgical TRUP (transurethral resection of the prostate), laser ITT (interstitial thermal treatment), radioactive seed implantation and electroporetic drug delivery [Wu et al., 2001; Lim et al., 2000].

![Figure 4-9: The URObot.](image)

(Adapted from [Wu et al., 2001])
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In 1993, a special purpose neurosurgery robot was developed at the University of Lausanne [Glauser, 1995]. Project MINERVA is a CT scanner based robot, which is capable of performing surgical procedures without any direct human intervention (Figure 4-10).

![Figure 4-10: The robotized MINERVA system.](Adapted from [Glauser, 1995])

*The patient is scanned by the CT machine. The robot registers the location of the treatment site and moves itself into the correct position and orientation. The surgical tools move down a linear track to the target site.*

The ROBODOC hip surgery robot is a good example of an orthopaedic robotic surgery system [Taylor et al., 1999]. It is based on a SCARA type robot. In traditional hip replacement surgery, the surgeon "hand carves" the femoral cavity for the implant. The shape of the cavity is often incorrect, resulting in ill fitting implants. Developed by Integrated Surgical Systems Inc., ROBODOC can automatically create the precise cavity for the implant (Figure 4-11).
Recent research has been into the use of robots designed to work in close partnership with the surgeon. The ACROBOT (Active Constraint robot), developed at Imperial College [Harris et al., 1998], is an example of such a robot. It is used in total knee replacement surgery. Under the control of a computer system, the robot is allowed to operate by the surgeon within a set of constraint boundaries that constitute a safe cutting area and provides the correct cutting planes for a good prosthesis/bone alignment. It is back-driven by the surgeon and offers little resistance to his drive so loop the desired safe boundary is not exceeded. Great resistance prevents back-driving when the surgeon attempts, knowingly or unknowingly, into unwanted region. ACROBOT represents a new type of robotic system for surgery, known as a 'synergistic' system, in which the surgeon's skill and judgement are combined with the robot control constraint capabilities to form a partnership that enhances the performance of the robot acting alone (Figure 4-12).
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Figure 4-12: ACROBOT Knee-Surgery Robot.

(Adapted from [MIM, 2002])

The surgeon guides the movement of a rotary cutting tool (A) over the femoral head (B) of the knee joint. ACROBOT (C) will only allow movements within a set boundary (set in pre-operative planning) to create the accurate profiles needed for the implants.

Figure 4-13: Tele-manipulator system developed by ISS.

(Adapted from [Intuitive Surgical, 2002])
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The surgeon (A) moves master manipulators at the Master Control (B) which incorporates display unit that provides visual feedback of the surgical site. The slave manipulators (C) mimics the surgeon's movements. Another important advantage of these systems is the scaling (either up or down) of the surgeon's forces or movements onto the slave manipulators.

Another application of robots in surgery is with tele-manipulation systems (often referred to as tele-intervention, or tele-presence systems). This is the application of information-based technologies to deliver procedural health care through an electronic interface. Indirect patient contact is implicit; however, the distance separating patient and physician may be insignificant, or great.

With continued ultra-miniaturisation of electronics, and drive mechanisms, tele-manipulators can get even smaller and more delicate. Custom devices can be designed to hold surgical instruments, retractors and even to provide extra microdexterity to a surgeon. Working through an endoscope in a minimally invasive procedure, surgeons will require immense dexterity. An excellent micro-surgeon working at a short distance operates with an accuracy of about \( \frac{40}{\text{microns}} \). This accuracy is reduced considerably when working at long distances required by minimally invasive techniques. There is now a robotic device under development, which will greatly increase the accuracy of micro-surgeons. It is believed that this technology would extend the capabilities of micro-surgeons and allow more surgeons to perform highly skilled procedures currently performed only by the best surgeons [Das et al., 1999].

A number of remote tele-manipulator systems are currently under development. Notable examples are the ARTEMIS project in Germany and the commercial DA VINCI system developed by Intuitive Surgical Systems Inc. (Mountain View, CA USA) (Figure 4-13). ARTEMIS is an advanced robotics and telemanipulator system to aid surgeons in planning, training and conducting minimally invasive surgery [Voges et al., 1997].

The most widely used and readily accepted robotic devices into the operation room must be the robots that hold and position laparoscopic cameras. Their acceptance is due to the fact that the robot is not used to cut or to move cutting tools and their motions are not
considered as potentially dangerous. These, small foot-print positional robots, replace the need for the surgeon's assistant to hold and manoeuvre the laparoscopic camera. This provides for a less congested environment around the operating table. Movement commands for these robots can be by foot pedals, head motion sensors or voice commands. Notable example of this type of robot is the AESOP system developed by Computer Motion Inc.

4.3.3 Surgical Simulators

One of the most actively researched fields of *Computers in Medicine* is the development of systems using medical imaging, computer graphics, bio-mechanical analysis, and virtual environments, to simulate surgery for medical education, scientific analysis, and pre-treatment planning.

The traditional teaching method that has developed for surgical training is based upon the preceptor or apprenticeship model, in which the resident surgeon learns with small groups of peers and supervisors, over time, in the course of patient care. Surgeons have always acquired most of their operative and judgement skills through this lengthy 'learning by doing' method. The recent crisis in health care has highlighted a dire need for timely and effective treatment and the need for many more medical specialists.

One of the methods to shorten the duration of the learning curve without comprising the mastering of surgical skills, is the computer-based world of Virtual Reality (VR) and simulators. The surgeon will now be able to hone his skills on simulated procedures, and does not have to rely on real patient operations for his education. These surgical simulators are ideally suited to the monitoring of progress and include 'playback' facilities to refine one's technique.

Some examples of these simulators are:-

- Nasal Endoscopic Simulator [Bockholt et al., 1999].
- Laparoscopic surgery simulation [Moutsopoulos et al., 1997].
- Endoscopic surgery simulation [Dumay et al., 1995].
- Intravenous catheter placement [Prystowsky et al., 1999].
4.4 Registration

A number of registration techniques have been briefly discussed in the preceding sections. This section will provide more information on this essential aspect of computer assisted intervention.

Many researchers propose the use of large expensive imaging devices such as CT and MRI directly in the surgical theatre (examples were given of the MINERVA and SRL systems). This approach removes the need for unique registration process and the targeting of the treatment site is inherent in the treatment procedure, with the image of the treatment being completed in real-time. However, these devices are not easily available in standard surgical theatres, and the imaging systems of radiology departments already have difficulty meeting current demands.

However, the choice of a registration technique is often dictated by the procedure being undertaken, e.g.

- In orthopaedic surgery, a relatively simple registration procedure of implanting metal screws in the bone is employed. The patient is then scanned (CT or X-ray), and the positions of the screws are noted and used for pre-operative planning and intra-operative registration and guidance [Harris et al., 1998].

- In neurosurgery, the brain is assumed be fixed relative to the skull, hence registration of the skull allows accurate guidance for neuro-surgical techniques. The patient is scanned with a special frame (stereo-tactic frame) is fixed to his skull by means of screws. Co-ordinates in the brain, relative to the frame, can be
measured and used for treatment planning and a surgical navigation [Kwoh et al., 1988].

- In maxillo-facial reconstructive surgery, registration is often achieved by landmark features on the skull or by registration devices clamped between the jaws of the patient.

- The registration of soft tissue poses the greatest challenge. In external radiotherapy, the method of choice is the use of partial body masks, with the appropriate target co-ordinates marked on it. This ensures that, on repeated visits, irradiation occurs at the same position. A novel method of using surface registration of the liver is currently being researched by a group at Vanderbilt University (USA). They propose using a grid of tiny laser induced lesions on the surface to provide a model of the liver for use in imaged surgery [Herline et al., 1999].

- At Nanyang Technological University, the prostate surface obtained from pre-operative MRI can be registered with intra-operative ultrasound images. By doing that, the cancer location information obtained from MRI images can be transferred to the robotic system which conducts ultrasound scanning [Wu et al., 2001]. This is briefly outlined in section 4.2.3.

Interest in image computing has greatly enhanced many of the registration techniques mentioned above. Faster computers and more complex software have resulted in many registration procedures evolving into intra-operative, real-time image guidance systems.
Chapter 5

ROBOTIC HIFU MANIPULATOR

5.1 Introduction

Recent studies have shown that high intensity focused ultrasound (HIFU) is an effective treatment against various diseases. However, the size of the focal region is small in comparison to the size of the tumour. For this modality to be effective on the entire volume of the tumour, the foci will be required to be moved in the $x$, $y$ and $z$ axes. The precise and safe movement of the focal region can only be achieved under computer (robot) control.

This chapter provides: -

- an overview of present manipulator-based HIFU systems;
- a discussion on the conceptual development of the required robotic manipulator, including design criteria for the final design; and
- a description of the detail design aspects of the robotic manipulator.

5.2 Present Manipulator-based HIFU Systems

HIFU ablation systems come in a number of different configurations, which are very dependent on the specific application. There are a few systems which incorporate some form of imaging/ targeting capability together with a manipulation device for positioning and/ or scanning of a single transducer. The complexity of these systems depends on the degree of manipulation, accuracy of the lesion placement and on-line monitoring of
temperatures and lesion creation. A brief description of three such systems will be provided.

5.2.1 MRI Prototype – Brigham and Women’s Hospital

The Focused Ultrasound Therapy research group at the Brigham and Women's Hospital, led by Kullervo Hynynen, is conducting clinical trials for the treatment of breast cancer using a prototype General Electric MRI-guided system [Hynynen, 1996]. The manipulator (hydraulically actuated positioning platform) is used to position a large single therapy transducer precisely under the tumour tissue while the patient lies on a water-filled polyethylene bag (Figure 5-1). The HIFU application system is accommodated in a water-filled operating table that can slide inside the closed magnet assembly of a standard MRI machine. The transducer can be moved in the x, y and z directions by a hydraulic positioning device within the water bath that acts as a coupling medium. The MRI serves two purposes: first, as a registration device in accurately determining the location of the treatment site; its second function is to provide the clinician with an interventional thermal map of the treatment site. This allows the clinician to monitor the temperature intensity and distribution in the region being treated.

Figure 5-1: Clinical prototype of a MRI-guided focused ultrasound surgery system developed by General Electric Medical Systems for the ablation of breast tumours.

(Adapted from [Hynynen, 1996])
There are no indications to whether this system will be expanded to include the treatment of other types of cancers. It is because propagation of an ultrasound beam is blocked by air or bone, e.g. liver, brain tumour, prostate etc. The major limiting factor of this present design is the inability of the transducer to be tilted (pitch and yaw movements), so that the therapeutic ultrasound beam could have greater access to other potential treatment sites. This will, undoubtedly, increase the complexity of the positioning system, which is possibly limited by the available technology in MR compatible components. The advantages of this system, however, are the good positional accuracy in the registration of the treatment site, and intra-operative monitoring of the heating (and hence destruction) of the tumour tissue.

5.2.2 The Sonablate™ and Ablatherm™ Systems

The Sonablate™ system is developed by Focus Surgery, Inc. Indianapolis, USA and the Ablatherm system is developed by Technomend International, Lyon, France. Both devices are the intra-cavitary HIFU device for the non-invasive treatment of benign prostate hyperplasia. The Sonablate™ system uses single transducer which incorporates proprietary transducer technology that provides for the imaging for treatment site and for ablation (Figure 5-2). On the other hand, The Ablatherm system uses two separate transducers, one for imaging and another for HIFU therapy (Figure 5-3). In both systems, the transrectal probe houses the actuators for the two DOFs movement (linear and rotational) of the small focused transducer (Figure 5-4). Interchangeable fixed focal length transducers determine the depth at which prostate tissue can be treated. The unit also incorporates a circulating cooling system, to possibly prevent burning of the rectal lining. In Sonablate™ system, a manually locked gross positioning arm holds the probe in the correct altitude during the procedure whereas in Ablatherm™ system, the probe is built-in and held by operating bed.

It is reported that the treatment process begins after the clinician defines the area of periurethral tissue that is to be ablated. Proprietary computer software provides the treatment plan for the destruction of "sectors" of tissue (Figure 5-4). By overlapping sectors under computer control, a new urethra can be created from the bladder neck to the verumontanum.
The Sonablate™ system has completed Phase III clinical trials for the treatment of BPH, and has been submitted to the Food & Drug Administration (FDA) for approval [Focus Surgery, 2003]. Both HIFU therapy systems are being expended to the treatment of localized prostate cancer [Gelet et al., 2001; Focus Surgery, 2003].

![Figure 5-2: The Sonablate™ made by Focus Surgery Inc.](Adapted from [Focus Surgery, 2003])

![Figure 5-3: Ablatherm™ system made by Technomed International, Lyon.](Adapted from [EdapTechnomed, 2002])
Figure 5-4: Probe mechanism in rectum.

Diagram shows how overlapping focal lesions are created in lateral and longitudinal patterns to ensure thorough necrosis in the target region of the prostate.

5.2.3 The Marsden HIFU System

This team at the Royal Marsden Hospital/Institute of Cancer Research, London, lead by Dr. Gail ter Haar, is actively researching the use of focused ultrasound for the ablation of tumours, e.g. bladder, liver etc. [ter Haar, 1998]. The system consists of a 1.7MHz, 10 cm diameter spherical bowl therapy transducer, with a focal length of 14 cm, fixed to the end of a manual manipulator. It is located above the patient, and is capable of being positioned with five DOFs (Figure 5-5). Acoustic contact with the skin is achieved through a small bag of degassed water. Targeting and registration are achieved by a commercially available ultrasound diagnostic system. Once the registration is achieved and the datum points noted, the diagnostic transducer is removed and replaced with the therapeutic transducer. Encoders, fitted to all linear axes, allow the monitoring of the movement of the transducers.

This HIFU system, however, does not have any on-line monitoring of the intra-operative temperatures of the creation of the lesions. It is reported that the lesions created are not immediately visible to ultrasound [ter Haar, 1998], unless they contain gas. An indication
of the efficacy of the treatment is the appearance of cyst-like structures detected in ultrasound images taken 10 days after the ablation procedure.

![Marsden HIFU manipulator](image)

**Figure 5-5: The Marsden HIFU manipulator.**

(Adapted from [Sutha, 1999])

5.2.4 The prototype ULTRABOT system

The prototype ULTRABOT (ULTRAsound roBOT) system, which is developed by Selvan Pather of Imperial College, is designed for the treatment of Liver Tumours using HIFU. This HIFU system comprises of small multiple transducers which are attached to the end of the manipulator (Figure 5-6). The axis 1, which allows for translational motion, allows the focal region to ablate tissue at different depths. The rotational motion axis 2 and the linear motion axis 3 allow the focal region to ablate a layer of tissue in the profile of a partial cylinder. The axes 1, 2 and 3 will ablate tissue similar to the layers of an onion. The axes 4, 5 and 6 are rotational axes located at the end of the arm supporting the three transducers [Pather et al., 2002]. The method of registration, which uses an ultrasound diagnostic transducer, was incorporated into the therapeutic transducer using the same manipulator (Figure 5-7). To rotate the scanning arm through an angle, the diagnostic
transducer is deployed and the treatment site can be registered. The reverse rotation of the scanning arm moves the therapeutic transducer to ‘replaces’ the diagnostic transducer over the treatment site.

![Figure 5-6: The ULTRABOT.](Adapted from [Pather et al., 2002])

---

Rotation of Scanning Arm to deploy diagnostic transducer

Datum of AXIS 2

Fixed angular offset

Treatment site

Reverse rotation of AXIS 2 to align therapeutic transducers to treatment site

![Figure 5-7: Method of registration treatment site to therapeutic transducer.](Adapted from [Pather et al., 2002])
5.2.5 Multiple probes HIFU system

The multiple probe approach was introduced by As/P Sunita Chauhan in Imperial College for the neurosurgery [Davies et al., 1998]. The neurosurgery robotic system uses 3 HIFU probes which can position independently to any of 3 burr (entry) holes on the skull (Figure 5-8). There are 3 powered axes of motion for each HIFU probe viz. a pitch, a yaw and an in/ out relative to the pitched/ yawed mount. The HIFU probe is attached at the tip of the mount. A flexible bag containing the couple medium is attached to the HIFU probe.

![Figure 5-8: The modified head frame and motions of a single probe.](Adapted from [Davies et al., 1998])

The multiple probes approach has several advantages compared to conventional single transducer. The stray heating can be further reduced and the overlap foci area shows the significant temperature elevation. It makes the treatment more non-invasive. For the same spatial average intensity at the focal region, the intensity required for each probe is much lower (the exact value depends on the orientation of the probes). According to Chauhan, 3 probes give 2.5 times higher intensity than 1 probe. However, with the multiple probes approach, a larger aperture is required for the HIFU beam penetration. It is also very difficult to maintain the overlap foci area. The HIFU beam is deflected through multiple tissue layers and this makes the prediction complicated. As the tissue properties change when heated, the deflection of the ultrasound beam becomes unpredictable. In such a scenario, the overlap foci area becomes more difficult to achieve.
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5.3 Multiple HIFU Probes versus Single HIFU Probe

HIFU transducers come in different sizes. The larger the probe, the higher the power of the probe. This section discusses the considerations that go into using multiple smaller probes or a single large probe to bring about the same temperature rise within the prostate.

5.3.1 Multiple HIFU Probes

The fundamental concept of using multiple probes is to ensure that the focal point of each individual probe coincides at the one point. This consolidation of energy brings about a collective temperature rise at the focal point. This layout also reduces the stray heating. However, given the fact that HIFU beam would pass through inhomogeneous tissue layers on the way to the prostate and that tissue at higher temperatures would have altered ultrasound properties, it is likely that the beam may be deflected or diffused. As such, it would be difficult to focus multiple HIFU probes at the same spot. When this happens, the concentration of HIFU energy may not be sufficient to bring about the necessary temperature rise at the area of interest.

5.3.2 Single HIFU Probe

Employment of a single large probe would ensure the required temperature rise at the focal point. However, this approach also has the following disadvantages:

1. Stray heating effect.
2. Inhomogeneous tissue would cause the HIFU beam to deflect.
3. Temperature rise may alter tissue properties, which in turn may change the effect of the HIFU beam.

The stray heating effect is much dependent on the HIFU transducer technology. STORZ Medical uses a single probe transducer to focus deep into the kidney (to kill the kidney cancer cells) without stray heating in the medium of travel. This shows that the technology of transducer can overcome the stray heating problem.
Problems 2 & 3 can be overcome by online temperature rise measurement on the prostate. Once temperature rise is detected at the desired position, the HIFU transducer manipulator will move accordingly to the desired position. This online temperature feedback can ensure the final temperature rise at the desired position, taking into consideration beam deflections and tissue properties changes.

Seemingly, there are more advantages to using the single HIFU probe approach. As such, this approach was adopted.

### 5.4 Conceptual design of robot manipulator

Significant research is presently dedicated to the development of purpose-built surgical robotic systems. As compared to industrial types, these robots present distinctive features such as safety, sterility, and compactness making them appropriate for surgical environments. The reduced size, compact geometry and lightweight mechanical structure are important robotic features necessary for satisfying ergonomic requirements in the operating room. A unique feature of medical robots is their small work envelopes, which are developed for a specific treatment site. This, together with slower speeds, greatly enhances their safety and accuracy over industrial robots.

However, the compact design and small work envelop result in a severe shortcoming of many medical robots. The work envelope may be sufficiently large for the surgical procedure at hand, but is too small to provide global positioning over the patient from a floor-mounted base to the treatment site. A positioning and supporting device is thus required in order to locate the compact robot over the treatment site and to rigidly support it during the procedure.

To develop a robot manipulator to deliver HIFU beams accurately into the prostate, one has to consider various factors as follows:
**Location of prostate** – A TRUS probe will be used to acquire 2-dimensional images of the prostate. These images should be retrieved at constant, known intervals so that a 3-dimensional model can later be developed from the stack of 2-dimensional images. As such, the robot should be able to automatically translate the TRUS probe in and out of the rectum and full knowledge of the distance travelled.

**Location of cancer** – After locating the prostate, one should also know where the cancer cells are located within the prostate if a curative procedure is to be administered; in this case, HIFU. Magnetic Resonance Spectroscopy (MRS) imaging is a software enhanced version of the conventional MRI. It gives a chemical map of an MR image, showing the proportions of certain chemicals which are associated with prostate cancer. In doing so, one can tell, to a certain accuracy, the probable locations of cancer within the prostate. In the future, such information can be transferred and mapped onto the 3-dimensional ultrasound model of the prostate. With the information, the robotic system can even be manipulated to focus the HIFU beam at these cancer sites.

**Robot setup** – One should also consider how the robot should be moved and positioned with respect to the patient. This could be quite challenging since the TRUS probe is first inserted manually into the rectum and manipulated to obtain good ultrasound images. After which, the robot should be latched to the probe without altering its orientation.

**Good transmission of ultrasound beam** – There exists an air gap between the HIFU transducer and the perineal wall. A denser medium should be placed to fill this gap so that the ultrasound beam can be transmitted properly into the prostate. A custom made water bag may be a solution to this problem.

**Detection of temperature rise** – As in all processes, it is desirable to have a closed-loop system to ensure that the output is correct. In this application, it would be important to ensure that the temperature at the cancer site is risen appropriately. The future work may include the development of an ultrasound based non-invasive temperature sensing system which can be incorporated into this robotic system. The former would be able to sense the temperature rise at a selected location within the prostate.
**Usefulness of robot** – Besides manipulating the HIFU transducer to aim at the cancer site, one may consider further usefulness of the robot. This includes moving the focal point on the fly in accordance to acquired real-time information on tissue characteristics. The robot can also make repeatable positioning of lesions according to prostate volume and cancer distribution.

**Other considerations** – Other less urgent considerations of the robotic system include the detection of cavitation, compensation for secondary heating and reverberation from hitting the pelvic bone.

### 5.4.1 Preliminary design

Before commencing work on conceptual designs, it is very important to mention some constrains that had to be considered. Some of the initial considerations have been discussed in section 3.5.

- Spherical curve transducer will be used. It offers lower cost compared to phased array transducer.
- Due to obstruction of pelvic bone in the transperineal route, the opening window for the beam path must be as small as possible to prevent the interference with the bone. An active diameter of 54 mm was selected.
- Registration will be carried out using commercially available diagnostic ultrasound via the transrectal route. Custom made diagnostic ultrasound systems are very costly and will not be discussed in this project.
- As manoeuvring the transducer and probe requires position accuracy, it is proposed that servo motor, which can give the position feedback to the system, be used.
- A positioning and supporting device is required to locate both transducer and probe with respect to the patient on the operating table. A manually adjustable device is proposed as it is only positioned once when setting up the robot.
- The robot has to be designed in different modules to provide the ease of maintenance. Three modules are proposed; firing positioner module (for HIFU therapy), imaging module (for cancer localization) and manipulator module (for supporting and positioning).
5.4.2 Motion for the scanning of the focal region

The complete volume of the layer has to be scanned before the focal region can be retracted in the z direction (away from the patient). The thickness of the layer is defined by the length of the focal region. The pitch and yaw (revolute-revolute) configuration of the axis (Figure 5-9) would result in a very effective manipulator movement and create a spherical scanning pattern of the focal region. This spherical profile of the movement is appropriate for a majority of prostate tumour, especially in the peripheral zone, without encountering the bone. Another linear motion to the transducer in the direction away from the patient will allow the focal region to ablate layers of tissue at different depths. Therefore, three DOFs are required to manipulate the transducer.

![Partial spherical envelop created by pitch and yaw movements.](image)

5.4.3 Motion for the ultrasound scanning the prostate

In most robot assisted medical intervention, the robotic devices operate as open-loop systems. They rely on predefined knowledge of the location of the treatment site. To implement safe and effective treatment, the incorporation of transrectal ultrasound images to the therapeutic transducer is essential so that the precise location of the treatment area can be identified. The transverse ultrasound images can be used to incorporate with offline MRI/ MRS images to improve the quality of prostate cancer localization. The 3 dimensional ultrasound images can be produced from a series of 2 dimensional transverse ultrasound images. A series of 2 dimensional ultrasound images can be obtained by
transversely scanning along the TRUS probe axis (Figure 5-10). Therefore, only one
degree of freedom (DOF) is required to manipulate the TRUS probe.

![Figure 5-10: A series of transverse ultrasound images obtained from TRUS probe.](image)

### 5.4.4 Design of water bag

This section discusses the concept of the design of a water bag, which is required for
transmission of HIFU waves from the HIFU transducer to the perineal wall. Due to time
constrains during the candidature, the actual development of the water bag was not
performed. However a few concepts of how the bag should be designed will be presented
here.

The challenge of designing this water bag is to support a water medium between a
machine and the patient with variable length in between. Before looking at the water bag
concept, a mechanical support (see Figure 5-11) for a water bag is first designed.
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Figure 5-11: Mechanical support of the water bag.

Basically, the support takes the shape of a box with the top and one side wall absent and a hole made in the opposite wall to house the HIFU transducer. The water bag is placed inside the support. The opened side wall would allow the water bag to conform to the shape and contour of the perineal wall. Since the distance between the transducer and the perineal wall needs to be varied from 36 to 74 mm, the support would be made with a thickness of less than 36mm and be made to slide between the patient and the transducer.

1. Fixed Volume Bag Concept.

Figure 5-12: The fixed volume bag concept.
This concept requires a fixed volume of water to be sealed in a soft plastic bag. Depending on the distance between the transducer and the perineal wall, the bag would conform nicely to all supporting surfaces. In the case when the transducer is moved close to the perineal wall, excess part of the water bag would spill out of the support as depicted in the Figure 5-12.

2. Variable Volume Bag Concept.

![Diagram of Variable Volume Bag Concept](image)

Figure 5-13: The variable volume bag concept.

In this concept, the volume in the bag is variable. To maintain a constant water flow, input and output water hoses are connected to the bag as shown in the figure. When the transducer approaches the perineal wall, the volume of water required decreases. As such, the excess water escapes from the output hose. On the other hand, when the transducer moves away from the perineal wall, more water from the input hose is required to fill the water.
3. Swimming Goggles Concept.

![Diagram of Perineal Wall, Water Bag, and Seal]

**Figure 5-14: The swimming goggles concept.**

This concept follows the same principle of the swimming goggles. One side of the bag is opened and with its edge lined with a seal (rubber or adhesive). By pushing or adhering this end to the perineal wall, water can be contained regardless or the distance between the transducer and the perineal wall.

It seems that the swimming goggles concept has a slight edge over the other two concepts. It allows direct water contact at the perineal wall. This means that the HIFU beam passes from the transducer to the water medium straight into the perineal wall. Whereas in the former two concepts, the beam would have to pass through an additional medium, the water bag. Since the properties of HIFU changes each time it gets transmitted from one to medium to another, the lesser the number of transmission mediums, the more predictable the way the HIFU beam would behave.

### 5.4.5 Conceptual Designs

Before arriving upon the final design of the robot manipulator which will be presented later, various conceptual designs were considered. The final concept was selected after weighing the pros and cons of all possible designs. The following section discusses a few of these conceptual designs.
Different configurations of the HIFU transducer accessing the prostate via the transperineal route

1. Transducer facing up.

Example: Section 5.2.1, MRI Prototype – Brigham and Women’s Hospital

![Figure 5-15: Configuration with transducer facing up.](image)

The transducer could be designed to face upwards. In this scenario, the patient would be sitting up during treatment. The advantage of this layout is that the patient’s perineal area could be immersed in water so as to allow the transmission of HIFU. There is no need for a special bag to contain the water which acts as a medium of transmission. However, this layout would probably mean that robotic manipulator should be under water as well, which leads to much design difficulties. Furthermore, in the seated position, a lesser portion of the perineal wall is exposed as compared to when the patient is laying horizontally. This could be a drawback since the HIFU beam should be administered with an unobstructed view of the perineal wall so that beam does not infringe into other surround organs (penis and testicles).
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2. Transducer facing downwards.
Example: Section 5.2.3, The Marsden HIFU system and Section 5.2.4, The prototype ULTRABOT system.

![Configuration with transducer facing downwards.](image)

Figure 5-16: Configuration with transducer facing downwards.

If the transducer were to face downwards, the design of the robot would be simplified. Approaching from the top, it would be unobstructed and need not be immersed under water. The design of a water bag to act as a transmission medium is also simplified since, due to gravity, the bag would easily conform to the shape and contour of the perineal wall. However, this concept is not feasible as it would require the patient to be hung up side down, which is very uncomfortable and not practical.

3. Transducer facing horizontally
Example: other prostate treatment option like brachytherapy.

![Configuration with transducer facing horizontally.](image)

Figure 5-17: Configuration with transducer facing horizontally.
This configuration would be most comfortable for the patient. Accessing the perineal wall would be easy too since the patient’s legs could easily be shifted apart. The design of the robot would also be relatively simple since it need not be under water and has little space constrain. Furthermore, this configuration would allow for easy alignment of the patient with the robot and vice versa since the patient is in a stable position. However, as compared to the former 2 configurations, to cater for the water medium would not be as straight forward. If a water bag is to be designed, it should conform to both the surfaces of the HIFU transducer and the perineal wall and allows a variable distance in between at the same time.

Based on above considerations, the configuration with the HIFU transducer facing horizontally was chosen.

Route for ultrasound imaging of the prostate
This section considers the different possible routes to access the prostate for the purpose of ultrasound imaging.

1. via transperineal route
The greatest advantage of taking the transperineal route is that both the image capturing and HIFU administration procedures could be performed along this same route. Thus position integration would be fairly simple and straight forward. One of the drawbacks of this path is that comparatively, images obtained in this manner would not be as clear as those obtained via the transrectal route. Furthermore, the definition of cancer location using this route may not yield as good results as compared to other routes (e.g. transrectal).
2. via transrectal route
Using a transrectal probe to image the prostate is common practice for many other prostate related procedures (e.g. biopsy, brachytherapy). This proven method gives clear transverse and longitudinal images of the prostate. These clear images could be integrated with MRS images to pin point the location of cancers. Being in close proximity to the perineal wall, using this route would complement the design of a robot for transperineal HIFU access of the prostate.

3. via transabdominal
This route is too far from perineal area. Integration with a transperineal based HIFU transducer would be too complicated.

4. via transurethral.
This work space for this route is too small and thus would not be considered as an alternative.

Having considered all 4 possible routes to use for image capturing of the prostate, the transrectal route is chosen.

Positioning of both HIFU transducer and TRUS probe (Supporting manipulator)
This section explores the various ways for positioning both the HIFU transducer and TRUS probe simultaneously.

Option 1: Flexible linkage
Example: URObot

![Figure 5-19: The flexible linkage concept.](image-url)
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This concept uses a few linkages in series to support the transducer and probe. Flexibility is the main advantage of this configuration. However, it does not provide for high rigidity which is essential to provide for the necessary accuracy of the HIFU transducer.

Option 2: Direct support from the bottom

![Diagram of Direct support from the bottom]

**Figure 5-20: Direct support of manipulator from the bottom.**

This supporting manipulator provides base support for the transducer and probe. This configuration gives rise to a stable and rigid manipulator with a low centre of gravity. However, this structure is less flexible as compared to the flexible linkage option.

Comparatively, considering the nature of the application, rigidity is more important than flexibility. Therefore, option 2 is chosen.

5.5 Robot design

Based on the aforementioned specification, the assembly drawing of the robot is shown in Figure 5-21. The robotic system consists of three modules; firing positioner, imaging and manipulator modules. The firing positioner module comprises of the transducer and its manipulator. The aim of this module is to accurately position the transducer to fire at the specific cancerous location in the prostate gland. The imaging module carries the ultrasound probe for localization purpose. The cancerous location in the prostate is
localized by this module. The manipulator module helps to initially position the firing positioner and imaging modules with respect to the patient.

Figure 5-22 shows the proposed surgical planner of the robotic system. It describes the sequence of events that takes place during the actual surgical procedure. It also shows how different components and modules of the robotic system interact with each other.

The operation begins by using the manipulator module to position the robot with respect to the patient. Next, the imaging module manipulates a transrectal ultrasound probe to obtain transverse images of the prostate. These images would be processed to create a 3D model of the prostate. Using a graphical user interface, the surgeon would be able to define the area of interest in the prostate for intervention. Recent advances in imaging technology seem to give the possibilities of using magnetic resonance spectroscopy (MRS) to determine the locations of cancerous tumours in the prostate [Wu et al., 2001]. Having defined the area of interest in the prostate, the firing positioner module is activated to position the focal point of the HIFU beam at the particular point in space. The beam can also be made to sweep across a specific area in space with proper path planning.
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Figure 5-21: Assembly drawing of robot.

Figure 5-22: Proposed surgical planner.
5.5.1 The kinematics of the robot

Figure 5-23: (a) Firing positioner module and prostate; (b) Kinematics model of robot; (c) Firing positioner module photograph.

Figure 5-23a shows a possible position of the firing positioner module with respect to the prostate and Figure 5-23b shows the kinematics model of the robot. By means of the imaging module, a specific point (i, j, k) in the prostate can be defined with respect to the base frame (X₀, Y₀, Z₀). The firing positioner will have to position the HIFU transducer such that its focus point F coincides with point (i, j, k).
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The forward transformation matrix from the base frame to the HIFU transducer is calculated to be (Figure 5-23b):

\[
\begin{bmatrix}
\cos \theta_2 & -\sin \theta_2 \cos \theta_3 & \sin \theta_2 \cos \theta_3 & 0 \\
\sin \theta_2 & \cos \theta_2 \cos \theta_3 & -\cos \theta_2 \sin \theta_3 & d_2 \\
0 & \sin \theta_3 & \cos \theta_3 & d_1 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

where \( \theta_2, \theta_3 \) and \( d_2 \) are variables and \( d_1 \) is a constant. With reference to Figure 5-24, \( \theta_2 \) is the rotation of the HIFU transducer about the \( Z_2 \) axis and \( \theta_3 \) is the rotation of the HIFU transducer about the \( X_3 \) axis. The focal point of the transducer \( F \) is at a fixed distance \( d_4 \) from the origin of the last frame \( (X_4, Y_4, Z_4) \) in the direction of \( Y_4 \). The variable distance \( d_2 \) represents the distance between the transducer and the prostate and is controlled by a linear actuator. Therefore, with respect to the base frame, the point \((i, j, k)\) can be computed as:

\[
\begin{bmatrix}
i \\
j \\
k \\
l
\end{bmatrix} = \begin{bmatrix}
\cos \theta_2 & -\sin \theta_2 \cos \theta_3 & \sin \theta_2 \cos \theta_3 & 0 \\
\sin \theta_2 & \cos \theta_2 \cos \theta_3 & -\cos \theta_2 \sin \theta_3 & d_2 \\
0 & \sin \theta_3 & \cos \theta_3 & d_1 \\
0 & 0 & 0 & 1
\end{bmatrix} \begin{bmatrix}
0 \\
d_4 \\
d_1 \\
1
\end{bmatrix}
\]

which gives us 3 equations:

\[
i = -d_4 \sin \theta_2 \cos \theta_3 \\
\text{(Eq. 5-1)}
\]

\[
j = d_4 \cos \theta_2 \cos \theta_3 + d_2 \\
\text{(Eq. 5-2)}
\]

\[
k = d_4 \sin \theta_3 + d_1 \\
\text{(Eq. 5-3)}
\]
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Having 3 equations, the 3 variables $\theta_2$, $\theta_3$ and $d_2$ can be found by rearranging (Eq. 5-1), (Eq. 5-2) and (Eq. 5-3) in the following manner:

\[ \theta_3 = \sin^{-1}\left(\frac{k - d_1}{d_4}\right) \]  
(Eq. 5-4)

\[ \theta_2 = \sin^{-1}\left(\frac{-i}{d_4 \cos \theta_3}\right) \]  
(Eq. 5-5)

\[ d_2 = j - d_4 \cos \theta_2 \cos \theta_3 \]  
(Eq. 5-6)

![Diagram of a robotic manipulator](image1)

![Diagram of a robotic manipulator](image2)

Figure 5-24: Manipulator of the firing positioner mechanism.

5.5.2 Avoidance of mechanical clash

Due to the space constraint between the patient’s anus and the perineal area, the firing positioner and the imaging modules cannot function simultaneously. As such, the robot is
designed in a manner that when one of these modules is in use, the other will be shifted away to prevent any form of mechanical clashing. Figure 5-25 illustrates the possibility of mechanical clashing and how it can be avoided. Basically, when the imaging module is in use, the firing positioner module is lifted up 60 mm. On the other hand, when the firing positioner module is in use, the imaging module is shifted 125 mm to the side.

Figure 5-25: (a) Mechanical clashing of imaging and firing positioner modules; (b) Only imaging module in use; (c) Only firing positioner module in use.

P-prostate; R-rectum
5.5.3 Robot to patient alignment

The task of the rectal aligner is to aid in the alignment of the robot to the patient. It also prevents the prostate from moving during the intervention procedure. Figure 5-26 shows the mechanism of the rectal aligner.

![Figure 5-26: Mechanism of rectal aligner.](image)

It is primarily a hollow cylinder made of Teflon, which can transmit ultrasound with little absorption and reflection. A specially designed water bag wraps round the distal portion of the TRUS probe. The purpose of this configuration is to maintain a water and Teflon medium between the TRUS probe and the rectal wall since ultrasound scan cannot function well in an air medium. During the intervention, the surgeon manually inserts the rectal aligner into the patient’s anus. He then inserts the TRUS probe into the aligner and adjusts the orientation of the aligner so that the probe can capture the best images.

With the rectal aligner in place, the next step would be to position the robot to ‘hook’ onto it. The manipulator module is specially designed for this task. Primarily, it positions the firing positioner and imaging modules pre-operatively with respect to the patient using the rectal aligner as a guide. With reference to Figure 5-27, the manipulator module is first moved such that the hook-up platform is parallel with the rectal aligner. Having constrained this DOF, the manipulator has 3 other DOFs in the s, u and t directions. The right vertical arm is first adjusted in the u direction so that the hook-up platform has the same inclination as the rectal aligner. The hook-up platform is then moved in the s direction such that the hook-up point on the manipulator falls vertically below the hook-up point of the rectal aligner. Finally, the entire manipulator module is shifted in the t direction till the 2 hook-up points coincide.
5.5.4 Detail Design

5.5.4.1 Firing positioner module

Figure 5-28 shows the overall view of the firing positioner module. It consists of ‘p’, ‘q’ and ‘r’ motion mechanisms and the HIFU transducer holder. A ‘Connecting Bar’ is used to link the HIFU transducer holder to the ‘p’ and ‘q’ motion mechanisms. The ‘r’ motion mechanism is linked to the HIFU transducer holder. With such a linkage, ‘p’ and ‘q’ motions do not affect ‘r’ motion. However, the movement of ‘r’ will affect the motions of ‘p’ and ‘q’ simultaneously.

The HIFU transducer is inserted into a spherical bushing (THK model SA1 60) and locked at the other end. Therefore, HIFU transducer is held tightly inside the SA1 60 bushing (Figure 5-29). The HIFU transducer can be easily removed from the spherical bushing by loosening a ‘lock nut’.

A hollow brass rod is inserted into another spherical bushing (THK model PB 25) as shown in Figure 5-30. Brass was chosen as the material because it can produce sliding movement with the inner core of Spherical Bushing. The brass rod is then secured to the HIFU transducer.
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The distance (along the brass rod) within the two spherical bushings is fixed in the design. The position of the spherical bushing SA1 60 is fixed whereas the spherical bushing PB 25 is constrained to move perpendicular to the brass rod axis (Figure 5-30).

As a consequence, movement in the direction of ‘p’ or ‘q’ enables the orientation of the desired path of HIFU transducer. Translation of linear movement to rotate the HIFU transducer is achieved by using two motors.

![Diagram](image1)

**Figure 5-28:** 3D view of firing positioner module.

![Diagram](image2)

**Figure 5-29:** The transducer holder.
Figure 5-30: ‘p’ and ‘q’ motions.

Since slight movement of either ‘p’ or ‘q’ or both can produce significant changes to j and k coordinate of focal point, their movements must be of high precision to achieve an accurate focal position. Therefore, ball screws (2 mm/revolution) are selected as a medium to transfer the motor rotation to ‘p’ or ‘q’ directions (Figure 5-31). As a single complete rotation of motor results in one pitch movement, the movement can be achieved to very high precision. The use of Spur Gear was aimed to reduce the size of the robot. The Ball Screws were attached to produce ‘p’ and ‘q’ movements respectively. The same principle was applied for the ‘r’ movement (Figure 5-32).

Figure 5-31: ‘p’ or ‘q’ movement mechanism.
5.5.4.2 Imaging module

In order to produce movement along the probe axis, the TRUS probe holder is mounted on a ball screw and supported by a linear slide. The linear slide would ensure smooth linear motion of the TRUS probe. The ball screw is driven by a motor to produce movement along the probe axis (Figure 5-33).

The TRUS probe is held by the TRUS probe holder. The design of the TRUS probe holder is shown in Figure 5-34. The easily mountable holder can act as a reference point for the TRUS probe.
5.5.4.3 Avoidance of mechanical clash

Two kinds of movements are required; the lift-up of the firing positioner module and push-away of the imaging module. The movements are done manually and automatically locked (mechanical lock) at the desired positions. Both the firing positioner module and the imaging module are attached to a reference plate.

For the firing positioner module, there are two indexing plungers which are used to fix the position in the up and down positions. Linear slides are used to provide the lift-up movement (Figure 5-35).

For the Imaging module, an indexing plunger is fitted to the imaging module. Two stoppers are attached to the ‘reference plate’ to hold the ‘In’ and ‘Away’ positions. In
order to push the imaging module to the ‘away’ position, the indexing plunger is pulled up and moved to the other stopper position (Figure 5-36).

Figure 5-34: TRUS probe holder.
Figure 5-35: Firing positioner module: (a) down position, (b) up position.

Figure 5-36: Mechanism of ‘in-away’ position in imaging module.
5.5.4.4 Manipulator module

The adjustments of the manipulator are purely mechanical. All the mechanical motions in the manipulator module are manually adjustable by turning knobs. Fine-tuning capability can be achieved by converting the rotational motion to linear motion that can increase rigidity and reduce the applied force. The assembly view of the manipulator is shown in Figure 5-37.

![Assembly view of manipulator module.](image)

To produce ‘s’ movement, a screw thread block is attached to a plate (reference plate). The ball bearings are connected to a ‘s’ base plate in order to provide support for the tuning knob. When the ‘turning knob’ is turned, it moves the reference plate linearly. Two mechanical locks are used for locking after achieving the desired position (Figure 5-38).

The ‘u’ motion mechanism design is shown in Figure 5-39. Two pairs of screws and nuts with different threading namely CW thread and CCW thread are used. Therefore, by turning the knob, both pairs of screws and nuts moved in opposite direction simultaneously to change the length of the whole assembly which results in ‘s’ movement.

For ‘t’ movement, the screw thread is used to lift-up the end position point. In this case, four shafts and four linear bushings are used to constraint the position in ‘t’ movement. Turning the knob results in the module being lifted up (Figure 5-40).
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Figure 5-38: ‘s’ motion design mechanism.

Figure 5-39: ‘u’ motion design mechanism.

Figure 5-40: ‘t’ motion design mechanism.
5.6 Feasibility Study of Robot

This section discusses the feasibility of placing the robot next to the patient for an actual HIFU treatment of the prostate. The objective of this study is to ensure that there are no spatial constraints during the operation of the robot.

Patient condition

![Sagittal View](image1)  ![Transverse View](image2)

**Figure 5-41: The patient in the lithotomy position.**

The patient is placed in the lithotomy position during the procedure, as shown in the Figure 5-41. Both legs are opened wide supported by support fixtures. This position would fully reveal the perineal area and maximizes the working space of the robot.

Robot Work Space

1. Firing Positioner Module

As discussed in section 3.5.1, to fully access the prostate, the required distance between the transducer and the perineal wall ranges from 36 to 74 mm.
The firing positioner module consists of 3 motions; ‘p’, ‘q’ and ‘r’. Motions ‘q’ and ‘r’ are rotational motions about the transducer’s axes. They do not increase the work space of the robot during operation. The maximum value of ‘r’ is 78mm. This means that the maximum distance of the HIFU transducer to the perineal wall is 36 mm when ‘r’ position is pushed it to maximum. This position still falls into the required range of the distance between the HIFU transducer and the perineal wall.
Chapter 5: Robotic Manipulator

Should the robot move very close to the patient (face of transducer touching the perineal wall with ‘r’ pushed to its maximum position), the stroke length of ‘r’ would still manage to cover the range of 36-74 mm from the perineal wall. This flexibility of the robot’s reach is illustrated in the Figure 5-43.

![Figure 5-43: Transducer face touching the perineal wall with ‘r’ pushed to its maximum position.](image)

Figure 5-44: Top View, horizontal space required for firing positioner module.

As illustrated in the Figure 5-44, the robot requires at least 152mm (frontal view) when it is positioned just next to the perineal wall. Similarly, from the sagittal view, the robot would take up 117mm. Thus, even in its worst case (when the robot is in direct contact
with the patient), there is still sufficient space to operate motions ‘p’, ‘q’ and ‘r’ (see Figure 5-45).

2. Imaging module and manipulator module.
There is no space related issue concerning the imaging module. This device, which pulls and pushes a TRUS probe into the patient’s rectum, has been used in other robotic system effectively. Finally, the manipulator module is situated far from the patient and does not come in direct contact with him. Like the imaging module, it too does not pose any space related problems.

From the above considerations, it can be concluded that the HIFU robot can be comfortably placed at the perineal area of the patient and is capable of accessing the entire prostate.

5.7 Desired options

In the robotic system discussed, due to the apparent mechanical clashing, the TRUS probe and the HIFU transducer are used one after the other. Obviously it would be desirable to use both instruments simultaneously. To do this, the TRUS probe may be tilted...
downwards to allow more space for the HIFU transducer to manoeuvre. However, this may affect the quality of ultrasound images acquired if the TRUS transducer does not come in proper contact with the rectal wall. Another desired option would be to incorporate the imaging and therapeutic ultrasound transducers as a single entity.
Chapter 6

EXPERIMENTAL ANALYSIS: HIFU CALIBRATION

6.1 Introduction

The experiments aim to verify that the HIFU works accordingly to fulfil the requirement of this project. By doing that, the HIFU can be ensured to be an effective treatment, in this project, for the prostate cancer disease. As a non-invasive treatment, the ultrasound emitted from the transducer must be focused accurately to the target and cause it to elevate to the desired temperature (60–80°C). The intervening and overlying tissue should not be overheated which may cause damage to the healthy tissue. The experiments would also give light to how HIFU energy is absorbed by the tissue as the beam travels to the prostate. The temperature rise of tissue in between the HIFU transducer and the focus point would be investigated. The objective would be to ensure that stray heating does not occur and that if there should be a rise in temperature in the intervening tissue, it should not exceed an acceptable value. The temperature rise at the focus point would be investigated in detail. The main aim is to ensure that the temperature at this point can reach a predefined temperature regardless of the effects of the intervening tissue in between. To summarise, the experiments to be performed can be divided into three parts viz.:

- To investigate the temperature elevation at focal point;
- To investigate the temperature distributions along the beam path; and
- To investigate the temperature elevation in the *in vitro* specimens.

With the results of these experiments, one would be in a better position to understand the effects of a HIFU beam directed at the prostate transperineally. With this information, one can safely adjust the working parameters to bring about a controlled temperature rise at a

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\[†\] *In Vitro* literally ‘in glass’, a term used to describe a biological reaction which takes place under laboratory conditions.
predefined location in the prostate. Of course, there are other important factors to consider when applying the HIFU beam transperineally. These include the avoidance of hitting the pelvic bone and the urethra. The former problem has already been addressed in Chapter 3. The latter problem could be solved using robotic means: The urethra can be identified and outlined from preoperative MR images. From surface registration techniques, the MR information can be transferred into the intraoperative ultrasound images. Knowing where the urethra is, the robotics kinematics can be manipulated to ensure that the trajectory of the HIFU beam does not coincide with the position of the urethra. It is hope that with the advancement of MRS technology, the same method can be applied to locate the cancer sites within the prostate. Once again, the MRS information, with location of the cancers, can be mapped onto the ultrasound images of the prostate. The robotic system can be manipulated to focus the HIFU beam accurately and automatically at these sites.

6.2 Material and Methodology

A phantom, man-made object which mimics the organ of interest, is used to perform the investigation of the temperature elevations and distributions. In preparation of the phantom, the following considerations were made:

- The phantom should have ultrasound imaging properties similar to that of the prostate and intervening tissues. It is difficult to obtain phantoms with similar acoustic properties as human tissue. Commercially available phantoms which react similarly to HIFU as specific human organs are very expensive and are not used in this project.
- The phantom should be made with similar dimensions and shape as the prostate and intervening organs.

The use of phantom as specimen has an added advantage maintaining constant physical properties if there is a need for a huge number of tests to be performed. This is unlike real meat/organ, which varies in physical properties. The formula for preparing the phantom was carried out by a previous student which consists of tissue phantom and prostate phantom [Ang, 2001]. It showed the ultrasound images obtained were quite similar the
images obtained from real patient. From this statement, it is assumed that the phantom has similar ultrasound properties with real tissue.

6.3 Investigation of Temperature Elevation at Focused Point

The objective of this experiment is to investigate the variation of temperature elevation at the focused point with varying exposure time and input signal. In this experiment, two types of phantoms are used; prostate phantom and tissue phantom. Both phantoms are prepared in a box called phantom box. The procedure of the phantoms preparation is described in Appendix B.

Fixture Design Specifications/Requirements

- As per experiment objective, the temperature sensor (thermistor) should be located at the focus point of HIFU transducer.
- Temperature is to be measured from within the prostate phantom. Therefore, the thermistor should be embedded into the prostate phantom.
- No air gap is allowed in the preparation of the phantom as ultrasound waves cannot be transmitted through it.
- The HIFU transducer and the phantom should be immersed into the water which acts as an ultrasound transmission medium.

Design and Assembling Processes

Thermistor + Customized thermistor holder = Thermistor probe

Figure 6-1: The thermistor probe.
Chapter 6: Experimental Analysis: HIFU Calibration

The thermistor probe is made by inserting a thermistor into a custom designed hold. Epoxy glue is applied to secure the thermistor in place.

![Figure 6-2: The thermistor in the Phantom Box A.](image)

The thermistor probe is then screwed into the phantom box A as shown in the Figure 6-2.

![Figure 6-3: Preparation of phantom box A.](image)
Two layers of materials are used to develop the phantom. The first is a gelatine mixture (refer to Appendix B6-7) which represents the prostate. This mixture is introduced into the phantom box as shown above. After it has solidified, a second mixture is introduced. The latter, which has a different composition as the former, represents the tissue.

**Figure 6-4: The location of thermistor with respect to HIFU transducer.**

HIFU transducer and phantom box A are then mounted onto base plate A. The location of thermistor with respect to HIFU transducer is predefined. The height of the phantom box is such that the focus point of the beam falls along its centre line. Thus, the thermistor is positioned at the focus point of the beam.

**Figure 6-5: The assembled fixture immersed into a water bath.**

The assembled fixture is then immersed into a water bath as shown in Figure 6-5.
6.3.1 Experiment Setup

As shown in Figure 6-6, the experimental setup consists of the following items:

**Frequency generator** - The Frequency Generator sets the amplitude of the input power to the transducer whereas a switching circuit sets the exposure time of the power into the transducer. By varying the input voltage and exposure time, the temperature at the focal point of the transducer is recorded. Therefore, the variation of input voltage and exposure time affecting temperature elevation at the focused point can be investigated. For the specification of the equipment used, please refer to Appendix B.

**Oscilloscope** – The function of the oscilloscope is to verify the output signal of the function generator. The parameters to be monitored include frequency, voltage amplitude and root mean square (rms) voltage.

**RF power amplifier** – This instrument amplifies the signal from the function generator to a give rise to a power high enough to drive the HIFU transducer.
Switching circuit – This is specially designed circuit based on a programmable timer/counter (XR2240). This circuit switches the output of the frequency generator to the input of the power amplifier. By this means, the RF output power is fed to the transducer such that the transducer will generate ultrasound only when the switching circuit is activated.

Temperature sensor - The thermistor (temperature sensor) was placed at the predefined focal point of the transducer during the preparation of prostate phantom. Both transducer and phantom box are attached to a specially designed jig and submerged into the water tank. A Function Generator (Sampo FG1627) is connected to a specially designed switching circuit and then linked to the input of the RF Power Amplifier (ENI-A300) using BNC cable. The thermistor is linked to interface circuit and a data logger (RS components model number 830-053) in the computer. The output of the amplifier is connected to transducer.

As earlier shown in Chapter 3, the longest and shortest possible distances between the transducer and the perineal wall have been calculated as 74 mm and 36 mm respectively. Thus, for the experiment, the average distance of 55 mm has been used as the distance between the transducer and the tissue phantom. This distance would give a good representation of the real scenario. The thickness of the tissue phantom represents the thickness of the perineal skin, fats and muscle layers from the perineal wall to the prostate. Once again, by geometrical means (Chapter 3), a thickness of 56 mm was used to represent this layer of intervening tissue. The prostate phantom is positioned immediately after the tissue phantom. It takes the shape of a cylinder rather than the shape of a real prostate. This facilitates repeating the experiment with phantoms of constant geometry and shape since it would be difficult to make non-symmetrical objects of constant shape and size and placing them accurately at the same location.

6.3.2 Results

The graph for temperature elevation and input power with various exposure times is shown in Figure 6-7. There are four linear lines in the graph. The input voltage is in the range of 80 to 160 mV and the exposure times range from 1 to 4 seconds.
Chapter 6: Experimental Analysis: HIFU Calibration

Temperature elevation versus input voltage with various exposure times

Figure 6-7: Temperature elevation versus input voltage with various exposure times.

From the graph, the temperature elevations increase with increasing input voltage. The temperature elevations are also increase with exposure times.

6.3.3 Discussions

The graph shows linear relationship for temperature elevation and input voltage. Therefore, the input voltage can be predicted for the temperature elevation at the focal point. Higher input voltage and/or higher exposure time are required to elevate higher temperature at the focal point. However, if the exposure time is high, blood circulation in the body will cool down the heat and will make the temperature elevation unpredictable. The temperature elevation decreased after input voltage 150 mV. This is due to bubble formation at the surface of the phantom (in the path of the HIFU beam) that obstructed the propagation of HIFU. Since ultrasound waves do not propagate well in air medium, a lot of HIFU energy is lost due to these air bubbles. The result is lower energy intensity at the focal point which results in a lower temperature rise.
6.4 Investigation of temperature distribution along beam path

This experiment aims to measure temperature elevation at the points along the beam path. The motive of such an experiment is to ensure that the temperature of the small, controlled volume at the focal point is elevated accordingly. Beyond this volume, the temperature should remain under an acceptable limit. That is to say that if the HIFU transducer is fired at a cancerous region in the prostate, only the focused portion of the prostate should be heated to a point where cells are destroyed. Other than this small volume, all intervening tissue should remain at an acceptable temperature where healthy cells can continue to survive.

**Fixture Design Specifications/Requirements**
- To investigate the distribution of temperature, the temperature sensors (thermists) should be strategically distributed within the phantom in order to sense the temperature at difference locations along the HIFU path.
- The location of each thermistor should be known.

**Design and Assembling Processes**
Three thermistors are placed circumferentially with a fourth at the centre of the phantom box. All the thermistors have custom-made perspex holders to ensure that they do not reflect the HIFU beam. The former three thermistors are placed circumferentially at 120 degrees apart at a distance \( r \) from the centre.

![Figure 6-8: Thermistor placed at different \( r \) values.](image)
Chapter 6: Experimental Analysis: HIFU Calibration

Figure 6-9: Location of the thermistor probes in the phantom box B.

The radius \( r \) can be adjusted for different values from \( r = 3 \) to \( 7 \) mm. Due to the dimensions of the thermistors, the smallest \( r \) value possible is \( 3 \) mm. Smaller than this value, the thermistors would clash into each other. These possible thermistor positions cover a circle of radius \( 7 \) mm perpendicular to the face of the transducer.

Figure 6-10: Preparation of phantom box B.

The prostate phantom is then introduced into the phantom box after adjusting the positions of the thermistors. The procedure of the phantom preparation is described in Appendix B.
Chapter 6: Experimental Analysis: HIFU Calibration

Figure 6-11: The assembled fixture.

Similar to the former experiment, both HIFU transducer and phantom box B are secured onto a base plate B. The distance between phantom box B and the transducer can be adjusted by sliding the phantom box B along the base plate B. The jig is made in a manner where the fourth thermistor (situated at the centre of the phantom box) lies along the centre of HIFU beam path. Thus, in theory, it should sense the highest temperature, especially when the phantom box is placed at the focal length.

Figure 6-12: Special jig design for temperature distribution measurement.

The following step is to place both transducer and phantom box into the water tank as shown in Figure 6-12. The phantom box is placed at a distance 60 mm (indicated by the linear scale). Upon activation of the HIFU beam, the temperatures sensed by the four thermistors are recorded after a constant time interval. The phantom box is then shifted to
180 mm at intervals of 10 mm. The temperatures are recorded upon activation of the HIFU beam.

The experiment is repeated with the former three thermistors placed at \( r = 4, 5, 6 \) and 7 mm while the fourth thermistor remains at the centre of the phantom box B. A new phantom is prepared each time there is a change in the value of \( r \). The HIFU beam is activated and temperatures sensed by the thermistors are recorded. Similarly, the experiment is repeated with the phantom box shifted from 60 mm to 180 mm at intervals of 10 mm each.

For \( r =1 \) and \( r =2 \), only 1 thermistor is used. Otherwise, the thermistor will clash into each other.

### 6.4.1 Results

The graph obtained from temperature distribution along the beam path is shown in Figure 6-13. The graph shows the temperature at \( r = 0, 1, 2, 3, 4, 5, 6, 7 \) mm from the distance 60 to 180 mm from the transducer face. In this experiment, the input voltage is 180 mV and exposure times are kept at a constant 4 seconds. These parameters are randomly selected, as the main objective is to determine the temperature curve of the HIFU beam. The more important issue of this selection is the focal region and elevation to the desired temperature (60-80°C). The highest temperature achieved for \( r = 0 \) mm is at distance 128 mm. The temperature at the focus point rose more than 80°C across a distance of about 25 mm. For the other points, the temperature maintained lower than 60°C. At \( r = 0 \) mm, the temperature curve increases with distance up to the maximum at focal region and then decreases with distance to non-heated temperature. For \( r = 3 \) and 4 mm, the temperature curve increases with distance but decreases with distance before reaching focal region. The temperature curve continuously increases after focal region and then decreases to non-heated temperature. At \( r = 1 \) and 2 mm, the temperature curves are similar to that of \( r = 3 \) and 4 mm. The only difference is the temperature increase at the focal region. For \( r = 5 \) and 6 mm, the temperature does not change much showing that these regions are not affected by the HIFU beam.
6.4.2 Discussions

The results have shown that the temperature elevation is sufficient to destroy the tissue at the focal region. There is a great change of temperature in the focal region between $r = 0$ and $r = 1$. This means that the heating zone is localized. It does not affect/damage the nearby tissue since the temperature gradient is high. Considering the overall temperature curve, in the areas other than focal region, the temperatures remained lower than 60°C. At this temperature range, the healthy tissue will not be damaged for short exposures of the beam.

There are large variations between $r = 0$ and $r = 1$. From the graph, it can be observed that at position 90 to 140 mm for $r = 0$, the temperature increase is very high as compared to $r = 1$. This justifies that the beam will focus at the centre with diameter less than 2 mm. For $r = 1$, the beam does not pass through the thermistor. Therefore, it does not heat up.
From the graph, there are 2 small peaks for $r = 1$ to 7 where as only 1 large peak for $r = 0$. This phenomenon can be explained with the aid of Figure 6-14. The HIFU beam converges at 130mm then diverges again beyond that. As such, for $r=0$, the thermistor would record only one temperature rise. Whereas, for other values of $r$, the thermistor’s location could be within or outside the HIFU beam depending on the distance from the transducer. Thus, they would generally record two temperature rises. The highest HIFU beam density (smallest diameter of cross section) is at $r=0$, therefore it shows the largest temperature rise.

It can be concluded that when the HIFU beam passes through healthy tissue, the focal point of transducer will be heated up. The tissue along the path will also be heated up, but to a much lesser extent.

Figure 6-7 indicates the maximum temperature reached (at 4 secs) was under 60°C, whilst Figure 6-13 shows the central focus as 90°C. This is because the input voltage to the power amplifier is higher for experiment 2 (180 mV) (Figure 6-13) compared to experiment 1 (150 mV) (Figure 6-7). Furthermore, the thickness of phantom for experiment 1 is thicker as compared to experiment 2. Some heat has been absorbed which reduced the temperature rise.

One may notice that only the phantom box is made of the phantom material while the rest of the portion between the thermistors and the transducer is a medium of degassed water. This set up is to ensure a constant and repeatable environment for the tests. Since the tests yield acceptable results (only a small predefined volume if heated up beyond a threshold
Chapter 6: Experimental Analysis: HIFU Calibration

temperature), future experiments may be performed using real tissue. Due to the inconsistent properties of tissue, the heating mechanism may not behave as predictable as this set up. Different kinds of tissue may yield different results, which require different forms of compensation techniques to better the results. Furthermore, depending on the exposure time of the HIFU transducer, tissue properties may change which may give rise to more variations of the intended results. Thus, it is fair to say that the experiment described in this section is but a preliminary step to a ladder of more realistic experiments to be carried in the future. Probably, the best method to perform this validation is to use real human tissue from the perineal wall right up to the prostate. If results prove to be repeatable, software or mechanical means could be used to further improve the accuracy of the transducer.

Hence, the results in this experiment only show that the transducer can accurately bring about a rise in temperature of a small, predefined volume in a phantom material across a medium of degassed water. Further, more realistic tests should be performed in the future before one can conclude that the HIFU transducer is a credible non-invasive therapeutic tool that can be used to treat prostate cancer via the transperineal route.

6.5 Investigation of temperature elevation using in vitro meat specimen

The objectives of this experiment are:
- To investigate the temperature elevation in in vitro meat specimen.
- To investigate the lesion at focal point caused by HIFU.

Two types of experiment were carried out. One aimed to determine the temperature elevation on in vitro specimen. The other one is to investigate the lesion of the in vitro specimen after exposure to HIFU beam. These two experiments cannot be carried out together because the insertion of the thermistor will destroy the lesion of the in vitro specimen.
Chapter 6: Experimental Analysis: HIFU Calibration

**Fixture Design Specifications/Requirements**

Temperature elevation

- The HIFU focal point should be within the test specimen.
- As such, the temperature sensor (thermistor) should be embedded at the focus point inside the specimen in order to measure the temperature rise.

Lesion

- The test specimen should be dissected accurately along the central of the HIFU beam in order to view the lesions caused by the beam.

**Design and Assembling Processes**

*Temperature Elevation Measurement*

![Figure 6-15: The jig C.](image)

For the temperature elevation measurement, the *in vitro* specimen was placed in the jig C (Figure 6-15) and a thermistor was inserted vertically into it.

The position of the thermistor is predefined mechanically and coincides with the focal point of the transducer. The meat specimen is simply supported (without constraints) by the jig C. For better support, phantom material could be used to gel the meat specimen onto the jig. Similar to the earlier described experiments, the entire jig is immersed into degassed water. The HIFU with predefined parameters is fired at the *in vitro* specimen (Figure 6-16) and the temperature elevation was recorded.
Chapter 6: Experimental Analysis: HIFU Calibration

Figure 6-16: The jig for measuring temperature elevation of \textit{in vitro} specimen.

\textbf{Lesion Investigation}

Figure 6-17: The HIFU firing on the \textit{in vitro} specimen.

For the lesion investigation, the \textit{in vitro} specimen was placed in the same jig, but without the thermister. The HIFU is fired at the \textit{in vitro} specimen with predefined parameters (Figure 6-17).
Chapter 6: Experimental Analysis: HIFU Calibration

Figure 6-18: The custom-made blade and jig D.

After firing of the HIFU transducer, the *in vitro* specimen is sliced in the direction of HIFU beam. This performed with a custom-made blade, which uses the sides of the custom-made jig (as shown above) to cut the specimen in a vertical plane parallel to the direction of the HIFU beam. This cut will reveal a cross section view of the focal point within the specimen.

6.5.1 Results

Pork was used as an *in vitro* test specimen. For the temperature measurement (see the experimental set up in Figure 6-19), the temperature at the thermistor was recorded at 66°C. The input power was 180 mV and the exposure time was 4 seconds for this experiment. These parameters were predefined from the temperature distribution measurement. If the experimental results showed that the heat generated was insufficient, these parameters may be increased. In the other experiment to investigate the lesion created by HIFU, the dissected meat showed a clear lesion with the above-mentioned parameters as shown in Figure 6-20.

6.5.2 Discussions

The HIFU beam elevated the tissue temperature at the focal region to 60-80°C. At this range of temperature, the protein contained in the tissue denaturalised, which can cause cell death. The fact can be verified from the lesion created from the same experiment. Only lesion could be seen in the focal region, while other areas of the tissue remained unaffected. This lesion signifies cooked meat, which is the desired result for the use of
Chapter 6: Experimental Analysis: HIFU Calibration

HIFU to treat prostate cancer. As a conclusion, there is a high potential for the HIFU beam to kill cancer cell in the biological soft-tissue.

Although this experiment showed desirable results, it would be incorrect to conclude that HIFU can indeed be used to treat prostate cancer transperineally. The experimental set up was an ideal case with consistent and simple mediums between the transducer and the target tissue. As explained in the previous experiment, the real situation would encompass firstly of a variable volume of degassed water, which forms an artificial medium for HIFU transmission from the transducer to the perineal wall. A layer of skin, muscles and fats follows this before reaching the prostate. To make matters even more complicated, the tissue properties are dynamic and changes from layer to layer, person to person. This experiment marks the beginning of a series of more realistic tests to further understand the effects of HIFU via the transperineal route. However, as a preliminary experiment, the results obtained were promising.
A hole is punched into the meat specimen for the insertion of thermistor.

The thermistor is inserted into meat specimen.

The meat specimen and thermistor are placed into the jig.

The HIFU beam is fired at the specimen.

Figure 6-19: The experiment set up for temperature elevation measurement (pork meat).
Chapter 6: Experimental Analysis: HIFU Calibration

The experiment set up for investigating the lesion caused by HIFU.

Pork Meat in Jig C

The lesion created by HIFU firing.

Lesion

Figure 6-20: The experiment for lesion investigation (pork meat).
Chapter 7

CONCLUSIONS & FUTURE WORK

7.1 Conclusions

The opening chapter, which forms the skeleton of this thesis, briefly discusses the nature of the problem and projects a vision of the solution in the form of concisely defined goals and objectives. There is growing concern regarding the increasing incidence of prostate cancer as the proportion of the global elderly population increases. An effective, easy to administer and cost-effective treatment needs to be extensively implemented. Presently, there are a number of potential thermotherapy modalities, with emphasis on minimally- or non-invasive procedures. HIFU surgery is one example of a non-invasive treatment modality that is proving to be an effective clinic-based modality in the fight against prostate cancer. However, this modality can only be effective if the relatively small focal region of the ultrasound can be accurately scanned throughout the entire volume of the tumour. Subsequently, three objectives of this project arise; to study the feasibility of delivery HIFU via the transperineal route; to study the effectiveness of a selected HIFU transducer namely Imasonic, France; to devise a robotic manipulator to deliver HIFU to treat prostate cancer.

A literature review has been presented. It has drawn attention to medical issues relating to the prostate and prostate cancer. The survey comprises the prostate anatomy and physiology, the risk factor of the prostate cancer, diagnosis and grading, staging followed by current treatment options. The application of thermotherapies in the fight against cancer is receiving unprecedented attention, with many research centres reporting promising results. The study also identified HIFU as the only non-invasive modality that could cause trackless lesions in deep-seated tissue thus making it well suited as a clinic, outpatient-based modality.
Chapter 7: Conclusions & Future Work

Following this, a review of the use of ultrasound in medicine, the methods of generating focused ultrasound beams and the details of biological effect that HIFU induces in deep-seated tissue. The possible treatment route using HIFU was discussed and selected. The transducer necessarily has to be custom made. In order to fabricate it, three parameters were estimated viz. frequency, focal length and active diameter of the transducer.

The part ‘Image Guidance and Robots in surgery’ was subdivided into two distinct specialist fields to present, viz. medical imaging and robotic systems in medicine. The requirements for a method of registration necessitated a comparison of the medical imaging techniques that are presently in use. Diagnostic ultrasound, which is widely used, relatively cheap and the modality of choice for soft tissue investigation, was chosen as the registration tool for this project.

The use of a number of HIFU systems was then discussed. To implement the first objective, to design a robotic manipulator for the effective scanning of the focal region of the transducer throughout the tumour, the conceptual design of the robotic system has been studied. The transducer was mounted on a mechanism which is capable of manoeuvring the transducer to give a partial spherical envelop. This envelop avoids possible obstruction to the HIFU beam by the pelvic bone. A series of 2D ultrasound images can be obtained by transversely scanning along the TRUS probe axis. Three DOFs are required for the transducer whereas only one DOF is required for the probe. Since there is a clash between transducer and probe, transducer can be lifted up 60 mm to clear the space for the probe operation. Similarly, the probe can be moved 125 mm away to provide space for the transducer operation. A position manipulator can position the firing positioner and imaging modules to the desired location with fine tuning capability. A ‘rectal aligner’ is designed as a guide to align the robot in a desired manner with respect to the patient. A water bag, which will be included in the future work, is required to provide a continuous acoustic propagation medium between the perineal skin and the transducer. Hence, the robotic system consists of firing positioner module, imaging module and manipulator module. The ‘rectal aligner’ and water bag are considered parts of the robotic system.
Chapter 7: Conclusions & Future Work

Tuning of HIFU transducer has been carried out. Three kinds of experiment have been conducted. The first is to investigate the variation of input power and exposure time affecting the temperature elevation at the focused point of transducer. The results showed that temperature elevations are increased linearly with both increased of the input power and also increase of exposure time. The next experiment is to investigate the temperature distribution along the beam path. It is to ensure that stray heating can be avoided which could damage the healthy tissue. In this case, only selected input power and exposure time is investigated. The last experiment is to investigate the temperature elevation at the focused point in the dissected prostate.

It can be said that HIFU is most effective for early stages of cancer growth and the scope of the present work focuses as such. From this project, one may not conclude that the transperineal route may is a feasible way to treat prostate cancer using HIFU. However, from the experiments carried out, the following conclusions can be made:

- Direct hitting of the pelvic bone can be avoided. By choosing an appropriate diameter of the HIFU transducer, all portions of the prostate can be reached by the HIFU beam without interference with the pelvic bone. This has been verified using data from the Visible Human Project.
- Heating in phantom/meat specimen can easily attain a temperature of 80 degrees C with only a few seconds of exposure times. Furthermore, this high temperature (which is high enough to kill living cells) is localised to a small, cigar shaped volume. The surrounding volume would remain at an acceptable temperature, which will not harm living cells.
- The focal point of the HIFU beam was not shifted despite using three types of medium (water, phantom material and meat specimen) with variable thickness.

The above-mentioned facts do support that proposal of using HIFU to treat prostate cancer via the transperineal route. However, there are more unanswered questions that need to be addressed:

- It is unclear if stray heating or a shift of the focal point may result when used in a real scenario where the HIFU beam must pass through an artificial medium of water, the perineal wall, fats and muscle and finally a portion of the prostate itself.
- Excessive heat may result at the skin interface, which may burn the skin.
Chapter 7: Conclusions & Future Work

- Reverberation may occur due to the pelvic bone.
- The feasibility of using a water bag has yet to be properly investigated.
- Validation of the temperature elevation within the prostate of a live patient. An ultrasound based temperature detection system may be developed in the future to ensure that the temperature elevation is as desired.

As such, it can be concluded the work done in this project thus far can only verify that the transperineal route using HIFU is feasible in an in vitro situation. More tests and clinical trials should be performed before one can conclude the feasibility of using HIFU to treat prostate cancer transperineally in humans.

7.2 Future Work

As can be appreciated, this project is on a robotic system for the application of HIFU for the ablation of prostate tumours, and as such the methodology pursued was based on diversity rather than great depth of analysis. Before the robot can actually be used in an actual clinical environment, various tasks should be performed.

7.2.1 Water bag design

As mention in section 5.4.4, a novel idea of a water bag design has been presented. It is a need to build-up the bag to ensure no water leakage occurs during the operation.

7.2.2 Motion control software

A motion controller is required to move the motorized parts of the robot. The control system needs to be developed to first traverse the TRUS probe in and out of the rectum to capture the ultrasound images of the prostate. The areas of interest in the prostate will then be defined. Following this, the HIFU transducer will be manoeuvred such that it focuses on the defined area of interest. Given a volume of interest in the prostate, the HIFU beam will begin firing at the furthest point with respect to the perineal wall. The transducer will
then be mechanically moved away from the perineal wall to allow the beam to be fired at the frontal portions of the prostate. It is suggested that the Visual C++ programming language should be used with Galil motion control card (model no. DM1845) in conjunction with an encoder (ICM2900).

### 7.2.3 Clinical trials

Clinical trial is an experiment performed on live human or animal. It is also known as *in-vivo* test. In this project, the clinical outcome of the patient is still unknown. One of the objectives of this trial is to find out or predict the outcome and the problems encountered during the operation. Another objective is to evaluate the effectiveness of the clinical device during the operation.

The persons involved in the clinical trial are medical doctors and engineers, depending on the objectives of the clinical trial. Matters related to medical issue should be addressed by medical doctors whereas the matters relating to engineering should be addressed by engineers e.g. positioning accuracy, temperature elevation etc.

Before reaching the clinical trial stage, other types of tests have been performed as depicted in the Figure 7-1.

![Figure 7-1: The experiment to clinical trial stage.](image)

Firstly, there is what is known as the phantom test. A man-made object, which mimics the organ of interest, is used to perform the test. If there is a need for a huge number of tests, the phantom test has an added advantage maintaining constant physical properties. This is unlike real meat/organ, which varies in physical properties. To confirm the results of the
phantom test, \textit{in-vitro} tests have also been performed. The results from \textit{in-vitro} tests are more realistic. With promising results from the \textit{in-vitro} test, animal test and cadaveric test will be carried out before the real human trial.

In this project, “Robotic HIFU for the treatment of prostate cancer”, the objectives of the clinical trial are as follows (from an engineering point of view):

- To determine if the HIFU focuses accurately at the target point with a given path.
- To determine the accuracy of the TRUS image calibration.
- To determine if the temperature at the focal point is elevated to the desired temperature with a given path.
- To determine the temperature distribution along the path of the HIFU beam to ensure no secondary or unintended heating.
- To determine the lesion size created by a single fire of the HIFU beam.
- To determine the heating effect at the skin interface.
- To determine reverberation effects due to the pelvic bone.
- To determine the feasibility of a water bag as a medium for ultrasound transmission between the HIFU transducer and the perineal wall.

The robotic system, which consists of a HIFU transducer and TRUS probe, is used to check the accuracy of the position of the focal point of the HIFU beam. The targeted focused point is guided by ultrasound transverse images obtained transrectally. The temperature of the HIFU focal point can be elevated to a desired temperature whereby the intervening and overlying tissue is not overheated. From a medical point of view, the heated zone can kill the cancerous tissue in the prostate without side effects in the long run.
References
REFERENCES


References


References


References


References


Appendix A

DATA SET DEVELOPMENTAL PROCESS

The data used for the transducer’s active diameter determination was based entirely on the images from the Visual Human Project (VHP) acquired from the National Library of Medicine (NLM). There are 1878 images from each data set of MRI, CT and colour RGB photography, obtained from a male cadaver.

At first, the images were segmented to acquire the desired information such as size, position and orientation of the prostate, pelvic bone, rectum and perineal wall. This can be achieved either by developing an automatic segmentation algorithm or painfully outline the desired segment manually by hand. Manual segmentation was chosen as the effort and time spent to develop such software for automatic segmentation is tremendous.

The segmentation of the prostate, pelvic bone and rectum was taken from the colour RGB photograph data set as there was more information available in the 2048X1216 pixels resolution 24 bits colour of the RGB photograph data set.

The data received from VHP was in RAW Format, 2048 x 1216 Pixel where each pixel is equal to 0.33 mm. There are in all 1878 images each at 1 mm interval. From the images, it was realized that images from 884 – 972 mm (head down) cover the bladder neck to the perineal wall. The interval between slices was set at 2 mm thus reducing the segmentation to 45 images.

Segmentation Procedure

The segmentation procedure includes size reduction, black painting, selection of internal and white painting processes (Figure A-1). Adobe Photoshop version 6.0 was used for this segmentation procedure.
Appendix A

Data from VHP

<table>
<thead>
<tr>
<th>Size Reduction</th>
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<tbody>
<tr>
<td>Black Painting</td>
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<tr>
<td>Internal Selection</td>
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<tr>
<td>White Painting</td>
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</tbody>
</table>

Figure A-1: The segmentation procedure.
Appendix A

**Size Reduction:** Mimics™ was used to generate a 3D simulation model. Since application could not support 2048 x 1216 pixel data size, the image was cropped to 2048 x 1024 pixel data size. The cropped area did not in any way affect the relevant data.

**Black Painting:** Generate a new layer (Layer 1). The foreground of the colour picker was set to black (R:G:B, 0:0:0). With the Paint Bucket Tool ((Paint Bucket Tool) option, black pixel was painted over the area. Layer 1 was then hidden and the background activated.

**Internal Selection:** From the cropped image (background), the Magic Wand Tool (Magic Wand Tool) was used to select the area of interest by choosing the colour in the area.

**Paint White:** Generate another new layer (Layer 2). The Layer 2 must be placed above Layer 1. The foreground of the colour picker was set to white (R:G:B, 255:255:255). Once again with the Paint Bucket Tool (Paint Bucket Tool) option, white pixels were painted over the area of interest. Layer 1 was activated again to obtain the desired image.

The image was then saved in JPEG format.

**Image format conversion**

After JPEG format was obtained, it was converted to PGM format and COL format.

**Portable Graymap (PGM) Format** – the entire 45 segmented images in JPEG format was converted to gray scale images, PGM Format by using the Batch Conversion Utility. Under the hex code, the images comprising mainly 01s and FFs except for the initial headings and transition period as illustrated which depicts the contents of a typical PGM file (Figure A-2).
Appendix A

<table>
<thead>
<tr>
<th>COL Format</th>
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<tbody>
<tr>
<td>Here is an example on how Mimics™ reads a file. For a hex code of AB were to be registered by Mimics™, the input should be 0A0B (Figure A-3). The software reads the second hex code and skips the first. The source code for conversion to Mimics™ readable file was developed by Irwan (2001).</td>
</tr>
</tbody>
</table>

**Figure A-2:** The Hex code of a PGM file, view under Hackman Ver3.21.

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<th>COL Format</th>
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<td>ATTENTION: The Singapore Copyright Act applies to the use of this document. Nanyang Technological University Library</td>
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</table>

**Figure A-3:** The Hex code of a COL file, view under Hackman Ver3.21.
**3D Reconstruction**

**COL Format**

Mimics™ is a modelling software that constructs 3D model from slices of 2D images using the marching cubes concept.

The 45 image files (COL format) which contain only data in hex code (01s and 0Fs), are uploaded into Mimics™. The vital point to note here is the parameters entered into the program to ascertain the correct output. The image size, slice distance and pixel size are...
manually recorded into the program for computational task. The preview graphic confirms that the software registers the intended images (Figure A-4).

The image information was sent to the program and computation task executed. Mimics™ generated three views of the model (front, side and top view) and subsequently, a perspective view of what seems to be a solid 3D model. The 3D model was exported as IGS format. The IGS format would then be converted to AutoCAD 2000 format.

Reference

Appendix B
Appendix B

EQUIPMENT DESCRIPTIONS FOR HIFU CALIBRATION

B.1 Function Generator

The photograph of Function Generator (Sampo FG1627) is shown in Figure B-1. A BNC cable (impedance 50 Ohms) is connected to the input of Programmable Timer Circuit (Figure B-2). The frequency ranges with range setting is set to 1M (0.2 MHz to 2.0 MHz). The output of the signal is set to sine wave. The attenuator of –20dB is used as it can generate the working range of voltage output.

The frequency adjusts accordingly so that the frequency shows 1700.0 kHz. The amplitude of the signal, which is the parameter of the experiment, will be adjusted accordingly. The $V_{\text{rms}}$ of the output signal can be displayed in Oscilloscope (Figure B-3).
B.2 Programmable Timer

This is a Programmable re-triggered timer controller circuit. It has been built around XR 2240 and a comparator for re-triggering the timer. Timing pulses of specified time duration is achieved by the XR 2240 Chip. This has built in Timer (Similar to 555) and a counter. The timing duration say T is fixed by the values R (440 Ohms) and C (1Mfd.) The Time constant is defined by R X C and the timer will output continuous pulses for every RC Seconds. This will be further counted by the counter circuitry (built in XR 2240).

The number of counts to be made is set by a dip switch. It can be varied from 1 to 256. The high low going pulse obtained at the LM308 pin 3 is further used to control the switch relay circuitry which turns on the required device. The switching circuit is built using 2N 2222 switching transistor.

Figure B-2: The programmable timer circuit.
This pulse also stops the timer. The push button switch initiates the timer. Each time the switch is pressed the timer will start and the counter will counts number of pulses based on the dip switch setting and a control pulse is available to control the circuitry after N times the RC seconds. Also at the same time the timer switched off by the Control pulse.

The duration after which a control pulse is varied from 1 to 256 times RC. And easily set by a DIP Switch using different combinations of ON and OFF conditions of the switch.

**B.3 Oscilloscope**

![Oscilloscope](image)

Figure B-3: The oscilloscope.

The BNC cable connected from output function generator to input of programmable timer circuit is branched to oscilloscope using T-joint BNC connector. Therefore, the output signal from function generator can be measured and displayed on LCD oscilloscope. The amplitude of the signal can be clearly defined in the oscilloscope.

**B.4 RF Power Amplifier**
Appendix B

Figure B-4: The A-300 RF power amplifier.

The power cord (20 A) of the RF Power Amplifier is connected to the socket. Then, the main switch of the power is turning on. The output of the Programmable Timer Circuit is connected to the input of the amplifier. The output of the amplifier is connected to the HIFU transducer. After that, switch on the panel is turned on and leave it for a few seconds for warming up purpose. Then, press the button on the programmable timer to allow the relevant voltage amplified and delivered to the HIFU transducer.

B.5 Pico Temperature Recorder

The Pico Temperature Recorder, model ADC-11, is used for the purpose datalogging for temperature. The voltage from thermistor (output signal and signal ground) will be connected to ADC. The signal obtained from picosoftware is shown in Figure B-5. The minimum voltage showed the highest temperature achieved by the HIFU system at the focal point. The minimum voltage will then convert to temperature according to a calibrated conversion table in the thermistor data sheet.
B-6 Phantom preparation for the investigation of temperature elevation

The prostate phantom was molded with 19 percent gelatine by weight (19 g of gelatine and 81 g of water) [Ang, 2001]. 19 g of gelatine was poured into a measuring mug and mixed with 81 g of hot water (about 80°C). The mixture was stirred immediately with a fork to evenly dissolve the gelatine. In the process of stirring, the bubbles formed were disregarded; they were removed later with a spoon. Once the gelatine was dissolved to form a uniform solution, it was poured through the strainer into the phantom box until it filled up the desired cavity. A thermistor (10 kΩ @ 25°C) was inserted into phantom box through the hole at the top before pouring the mixture into phantom box. After which, the box was left aside for a while to ensure there was no leakage before being placed into the refrigerator for at least half of a day.

The tissue phantom was molded with 10 percent of gelatine and four percent of psyllium fibre by weight [Ang, 2001]. 25 g of gelatine and 10 g of psyllium fibre were well mixed in a mug before hot water was added. The mixture was stirred when the water level is low, so that lesser powder would coagulate into lumps which were impossible to break up if there were lots of liquid. The water adding and stirring processes were continued until the
Appendix B

whole solution was about 0.25 litres. The whole mixture was cooled until about 40°C. It is then poured into the phantom box contained prostate phantom. The bubbles on the surface were scooped out. The whole set-up was left to cool overnight, so that it would harden without refrigeration. The phantom was then ready for the experiment.

B-7 Phantom preparation for the investigation of temperature distribution

The prostate phantom is also molded with 19 percent gelatine by weight. 11.4 g of gelatine was poured into a beaker and mixed with 48.6 g of hot water. The mixture was stirred immediately with a fork to evenly dissolve the gelatine. Once the gelatine is dissolved to form a uniform solution, it was poured into the phantom box until it filled up the desired cavity. After which, the box was left aside for it to solidify.