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Declaration of Authorship

I, Seán Walsh, declare that this thesis titled, “Radiobiological Modelling in Radiation Oncology” and the work presented in it is my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed:

___________________________________________

Date:

___________________________________________
“Do what you can, with what you’ve got, where you are.”

Bill Widener

“The heights by great men reached and kept, were not attained by sudden flight, but they, while their companions slept, were toiling upward in the night.”

Henry Wadsworth Longfellow

“Adversity is another way to measure the greatness of individuals. I never had a crisis that didn’t make me stronger.”

Lou Holtz

“Always bear in mind that your own resolution to succeed is more important than any other one thing.”

Abraham Lincoln

“The secret of getting started is breaking your complex, overwhelming tasks into small manageable tasks, and then starting on the first one.”

Mark Twain

“Nothing in the world can take the place of persistence...Persistence and determination alone are omnipotent.”

Calvin Coolidge
Abstract

Biological models potentially offer the ability to predict the response of tumour control to irradiation. A tumour control probability (TCP) model with excellent radiobiological pedigree was developed and examined to predict the clinical response of intermediate risk prostate cancer to external beam radiotherapy (RT) for a variety of fractionation regimes. The model was fitted using the Nelder-Mead (NM) simplex algorithm. In-house organ deformation software was also developed to account for inter-fraction organ motion. The deformation code replicates realistic anatomical deformation through compression and expansion of organs at risk (OARs) based upon the displacements of the prostate. Monte Carlo (MC) methods have been demonstrated to be the best method of modelling radiation transport and dose deposition. MC methods provide a definitive method to quantify the accuracy of these techniques and the accuracy of the procedures used to assess them. This work implements a method to tune a linear accelerator model, in an efficient process. All of these models (TCP, MC and organ deformation) were then utilised to study the potential improvements offered by image guidance, margin reduction and dose escalation to uncomplicated tumour control probability (UCTP). The predicted biological effect of these combined factors was explored in both a phantom study and clinical prostate cases. The results showed that with image guidance, margin reduction and dose escalation, there potentially exists a significant improvement in the therapeutic ratio obtainable for intermediate risk prostate cancer patients.
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Seán Walsh
September 2011
Publications


S. Walsh, E. Conneely, M Foley, and W. van der Putten, “Est la réduction de la marge dans le cancer de la prostate possible? Une étude de modélisation radiobiologiques”, Cancéropôle grand ouest, oral contribution, (Berder island, France, 2010).


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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ADT</td>
<td>Androgen Deprivation Therapy</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
<td>ASTRO</td>
<td>American Society for Therapeutic Radiology and Oncology</td>
</tr>
<tr>
<td>bNED</td>
<td>biological No Evidence Disease</td>
</tr>
<tr>
<td>CAX</td>
<td>Central Axis</td>
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<tr>
<td>CM</td>
<td>Component Module</td>
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<tr>
<td>CN</td>
<td>Conformity Number</td>
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<tr>
<td>CPU</td>
<td>Central Processing Unit</td>
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<tr>
<td>CRT</td>
<td>Conformal Radiotherapy Treatment</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
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<tr>
<td>DBS</td>
<td>Directional Bremsstrahlung Splitting</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>DIL</td>
<td>Dominant Intraprostatic Lesion</td>
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<tr>
<td>DTA</td>
<td>Distance To Agreement</td>
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<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
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<tr>
<td>ECUT</td>
<td>Electron energy Cut off</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EUD</td>
<td>Equivalent Uniform Dose</td>
</tr>
<tr>
<td>FSU</td>
<td>Functional Sub Unit</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full Width Half Maximum</td>
</tr>
<tr>
<td>gEUD</td>
<td>generalised Equivalent Uniform Dose</td>
</tr>
<tr>
<td>GTV</td>
<td>Gross Tumour Volume</td>
</tr>
<tr>
<td>GUH</td>
<td>Galway University Hospital</td>
</tr>
<tr>
<td>HDR</td>
<td>High Dose Rate</td>
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<tr>
<td>IGRT</td>
<td>Image Guided Radiation Treatment</td>
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<tr>
<td>IMAT</td>
<td>Intensity Modulated Arc Therapy</td>
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<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Treatment</td>
</tr>
<tr>
<td>LDR</td>
<td>Low Dose Rate</td>
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<tr>
<td>LKB</td>
<td>Lyman-Kutcher-Burman</td>
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<tr>
<td>LQ</td>
<td>Linear Quadratic</td>
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<tr>
<td>MC</td>
<td>Monte Carlo</td>
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<tr>
<td>MLC</td>
<td>Multi Leaf Collimator</td>
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<tr>
<td>MMCTP</td>
<td>McGill Monte Carlo Treatment Planning</td>
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<tr>
<td>MPRC</td>
<td>Medical Physics Research Cluster</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>MU</td>
<td>Monitor Unit</td>
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<tr>
<td>NM</td>
<td>Nelder-Mead</td>
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<tr>
<td>NTCP</td>
<td>Normal Tissue Complication Probability</td>
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<tr>
<td>OAR</td>
<td>Organ At Risk</td>
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<td>OER</td>
<td>Oxygen Enhancement Ratio</td>
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<tr>
<td>PCC</td>
<td>Phoenix Consensus Conference</td>
</tr>
<tr>
<td>PCUT</td>
<td>Photon energy Cut off</td>
</tr>
<tr>
<td>PDD</td>
<td>Percentage Depth Dose</td>
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<tr>
<td>PO2</td>
<td>Partial pressure of Oxygen</td>
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<tr>
<td>PRV</td>
<td>Position Reference Volume</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QUANTEC</td>
<td>Quantitative Analysis of Normal Tissue Effects in the Clinic</td>
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<tr>
<td>RMSD</td>
<td>Root Mean Squared Difference</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root Mean Squared Error</td>
</tr>
<tr>
<td>RL</td>
<td>Right-Left</td>
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<tr>
<td>RT</td>
<td>Radiotherapy Treatment</td>
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<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiotherapy</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SF2</td>
<td>Surviving Fraction at 2 Gy</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-Inferior</td>
</tr>
<tr>
<td>SSD</td>
<td>Source-to-Surface Distance</td>
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<tr>
<td>TCP</td>
<td>Tumour Control Probability</td>
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<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
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<tr>
<td>TDP</td>
<td>Transverse Dose Profile</td>
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<tr>
<td>US</td>
<td>UltraSound</td>
</tr>
<tr>
<td>UTCP</td>
<td>Uncomplicated Tumour Control Probability</td>
</tr>
<tr>
<td>UCRT</td>
<td>Ultra Conformal Radiotherapy Treatment</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume Of Interest</td>
</tr>
</tbody>
</table>
Introduction

IRELAND has the highest rate of prostate cancer in Europe, with approximately 3,000 people diagnosed with the disease each year.

Figure I.1: European age-standardised incidence and mortality rates: In 2008, around 324,000 men were diagnosed with prostate cancer in Europe (EU-27). The lowest European rates are in southern and eastern Europe and the highest rates are found in northern and western Europe.
Prostate cancer is responsible for over 500 deaths per annum in Ireland.

Radiotherapy (RT) is one of four proactive treatments for prostate cancer.

- Surgery
- Radiotherapy
- Hormone-therapy
- Chemotherapy

The two most effective treatments of prostate cancer are surgery and RT. Surgery for prostate cancer is usually a radical prostatectomy. This is where the prostate is fully removed from the body. RT utilises the biological effects of ionising radiation. Radiation is harmful to both cancerous and normal healthy tissue, it is therefore of great importance that the practice of RT is tailored in order to ensure that optimal levels of radiation are delivered to the cancer site whilst sparing surrounding healthy tissue. This is the radiobiological and clinical basis for RT in Galway university hospital (GUH) today.

\textbf{Figure 1.2:} Siemens Oncor RT linear accelerator: The Siemens Oncor RT linear accelerator (Siemens Healthcare, Erlangen, Germany) can deliver a wide spectrum of RT treatments and is in use at GUH.
Experimental and theoretical studies in radiobiology have contributed to the development of the RT in three clear ways.

- Modelling: providing a conceptual basis for RT to explain observed phenomena, such as, radiosensitivity, repair, re-assortment, repopulation, and re-oxygenation. Mathematical models which reveal mechanisms and processes that underlie the response of tumours and normal tissues to irradiation, such as the tumour control probability (TCP) and normal tissue complication probability (NTCP) models.

- Treatment strategy: development of specific new approaches in RT, such as hypoxic cell sensitisers and high linear energy transfer RT.

- Protocols: advice on the choice of schedules of RT regimes such as fractionation and dose rate, or whether or not to use RT concomitantly or sequentially with other treatments.

There is no doubt that radiobiology has been very fruitful in the generation of new ideas and in the identification of potentially exploitable mechanisms. A variety of new treatment strategies have been produced, but unfortunately few of these have so far lead to demonstrable clinical gains. A notable exception being the conversion formulae for fractionation correction, based on the linear quadratic
Introduction

(LQ) model for cell survival. However, beyond this the ability of radiobiology to guide the radiation oncologist is limited by the inadequacy of both the theoretical and experimental models. It is therefore necessary to improve both the theoretical and experimental models used in radiobiology, both clinical and experimental data is crucial in this respect.

Treatment of prostate cancer by ionising radiation may be conducted through external beam therapy, brachytherapy and nuclear medicine. External beam therapy is the most commonly available treatment method. External beam therapy consists of high energy ionising particles being accelerated in a linear accelerator (linac) and directed at a tumour from outside the body. The ionising particles used in RT are typically photons and electrons. However, other particles are used in RT, such as protons and carbon ions. Linacs are usually capable of delivering multiple energies and modalities. RT will refer to external beam radiotherapy using photons only from here on in. The process of RT treatment can be commenced, once a patient has been diagnosed with prostate cancer and the decision to treat the patient using RT has been made. Initially an accurate anatomical image of the patient is obtained using a computed tomography (CT) scanner, this is required to plan the patient’s treatment.

![Figure I.4: Siemens Somatom Sensation CT](image)

The CT scan provides an electron density distribution of the patient, required for dosimetry calculations. The treatment of each patient is meticulously planned using the digital imaging and communications in medicine (DICOM) standard
and a treatment planning system (TPS). The plan, based on the assessment of dose volume histograms (DVHs), is next approved by the treating oncologist and treatment of the patient begins using a linac. Linacs are manufactured by a number of different companies. Modern linacs are computer controlled and have numerous moving mechanical parts such as the gantry, jaws and multi-leaf collimators (MLCs). RT treatment is optimised through the precise control of these mechanical parts, which enable adapted individualised treatments to be delivered to any given patient, thus maximising the radiation dose delivered to the tumour tissue, whilst minimising the radiation dose to the surrounding healthy tissues. Tumours and organs at risk (OARs) come in all shapes and sizes. An individualised treatment that is carefully shaped, or conformed, in this way is said to be a conformal radiotherapy treatment (CRT).

![Figure I.5: CRT treatment of a prostate patient at GUH: The dose distribution is that of a typical six field CRT prostate treatment at GUH. The treatment beams are delivered at 0°, 45°, 115°, 180°, 225° and 315°. The beams are weighted 0.250, 0.125, 0.125, 0.250, 0.125 and 0.125 respectively.](image)

The need to increase the radiation dose in RT treatment without increasing the dose to normal structures has prompted widespread adoption of CRT treatment techniques. However, as dose distributions increasingly conform to target volumes, they become more sensitive to treatment uncertainties, such as patient setup error and organ motion. The patient’s anatomy and position during the course of radiation therapy usually varies to some degree from those used for therapy planning purposes. This is mainly due to patient movement, inaccurate patient positioning, and organ motion. Consequently, the actual received
absorbed dose distribution differs from the planned absorbed dose distribution. The two scenarios of relevance are an insufficient dose coverage of the targeted tumour volume and an over dosage of normal tissues. Both cases potentially compromise the clinical results. Variations in patient position and movement can be minimised with the help of precise patient positioning systems and rigid immobilisation devices. However, for some anatomical sites, such as the lower abdomen, the internal motion of organs due to physiological processes presents a challenge. Motion of the tumour volume is commonly accounted for by the use of margins that encompass the tumour volume. Tumours that are subject to significant movements require large margins that may include critical normal structures in the planned irradiated field. These structures may subsequently hamper the application of the intended therapeutic dose. This issue is of particular importance in dose escalation studies. The use of smaller margins may, on the other hand, compromise the adequate absorbed dose coverage of the moving tumour.

**Figure I.6:** RT margins: ICRU reports 50 and 62 define the relevant terminology. First, the gross tumour volume (GTV) is defined as the volume containing demonstrated tumour. Second, the clinical target volume (CTV) is defined to enclose the GTV plus a margin to account for suspected tumour involvement. The planning target volume (PTV) is defined by the CTV plus a margin to allow for geometrical variations such as patient movement, positioning uncertainties, and organ motion.

Organ motion that occurs while the patient is being irradiated is labelled intra-fraction organ motion. Respiratory and cardiac motion are the main contributors to intra-fraction motion, which affects mainly organs of the thorax and abdomen.
Inter-fraction organ motion occurs when the position of the prostate alters on a daily basis. This type of motion is primarily linked with the organs of the digestive and urinary systems, namely the rectum and bladder. Other factors such as changes in the patient’s condition can also affect the relative position of the prostate, e.g. weight gain or loss. The principal cause of inter-fraction motion of the prostate is the variation in bladder and rectal fill, this leads to deviations in the relative position of the prostate. Organ motion has lead to the development of image guided radiotherapy (IGRT).

TPS software achieves the necessary conformality of the dose needed for treatment of the patient by delivering different beams of radiation from various orientations around the patient as well as utilising fine beam shaping. The dose that is delivered to a patient, based upon TPS dose calculation algorithms, during irradiation with megavoltage photons is deposited by electrons which induce tracks of ionisation in tissue. The two quantities that determine the conversion between energy fluence and dose deposition are the total energy released in mass (terma) by the photon beam and the energy deposition pattern (kernel) around a photon interaction point. The two principle dose calculation algorithms are the pencil beam kernel model and the collapsed cone kernel model. In the pencil beam kernel model the point spread kernel is integrated along the radiological path of the beam. The result is stored as a pre-calculated analytical expression in the beam model. A pencil beam kernel model can only account for density variations and beam hardening along the radiological path in the dose calculation. The collapsed cone kernel model is based on a simplified form of a point spread kernel. The point spread kernel is subdivided into a number of cones that together constitute a $4\pi$ solid angle. The transport of recoil electrons as well as scattered photons that occurs inside each cone is integrated and collapsed on the central transport axis of that cone. Transport is then calculated only along the transport axes. Beam hardening and off-axis spectral changes are corrected for by adaptation of the effective attenuation coefficients that are applied to calculate the primary and scatter component of the terma. Patient treatment in RT can
be very complex and with this complexity comes a natural likelihood of errors in treatment. Consequently, there are rigorous quality control (QC) and quality assurance (QA) procedures, e.g., an independent dose check and checking of the transfer of parameters from the TPS to the treatment machine in every clinic, etc. This aids in minimising the likelihood of errors in treatment.

Figure I.7: Treatment planning: Medical physicists use sophisticated TPS along with their specialist knowledge to produce the optimum treatment plan for each individual patient. Every patient that receives RT treatment has a custom designed treatment plan.

A benefit of typical RT treatment is that treating over a period of weeks allows the correction of any small error over the length of a treatment if detected in sufficient time. Despite the best efforts in the clinic, there are limits to the accuracy associated with treatment at present. The sources of errors associated with treatment (Ahnesjo and Aspradakis 1999) are given in Table I.1. Considering the complexity of the dose delivery process, it is inherently difficult to attain great accuracy in practice and it is common to defer to the typical value of 5% as the level for corrective action (ICRU 1976). A prudent method for ascertaining the limits for dose calculation errors alone is to identify the other errors in the dose delivery chain and vary the dose calculation error to identify the limit where the overall value is seriously affected by the dose calculation error (Ahnesjo and Aspradakis 1999). Combining dosimetry estimates and delivery estimates as a representation of present techniques indicates that dose calculations do not need to be better than 2% with a correction action level at 4.6%. It is doubtful that radical improvements in the accuracy of dose delivery will occur in the immediate future, although some evolution should be anticipated. Developments in basic dosimetry, detector technology and accelerator stability could potentially reduce the errors in dose calibration, beam monitoring and flattening to half their
present values. Patient data and beam-patient set-ups are difficult to improve but a reduction to two-thirds of their present values should be possible. Summarising these expectations, a dose calculation accuracy of 1% will be sufficient as the ultimate future goal. Table I.1 displays numerous sources of error associated with patient treatment. Absorbed dose at calibration point refers to the uncertainty in dosimetry. Monitor stability and beam flatness refer to the uncertainty in stability in the linac output. Patient data uncertainties refer to the uncertainty in scanning of the patient. With the advancement of technologies, it has become possible to deliver increasingly complex treatments with ever improving accuracy.

| Table I.1: Errors associated with patient treatment (Ahnesjo and Aspradakis 1999) |
|-------------------------------------------------|---------|
| Error (%):                                      |         |
| Absorbed dose at calibration point              | 2.0     |
| Additional uncertainty for other points         | 1.1     |
| Monitor Stability                               | 1.0     |
| Beam flatness                                   | 1.5     |
| Patient data uncertainties                      | 1.5     |
| Beam and patient set-up                         | 2.5     |
| Overall excluding dose calculation              | 4.1     |
| Dose calculation                                | 1.0, 2.0, 3.0, 4.0, 5.0, |
| Resulting overall uncertainty                   | 4.2, 4.6, 5.1, 5.7, 6.5, |

RT treatment has progressed from simple co-planar treatments to CRT and now to intensity modulated radiation therapy (IMRT). CRT treatment uses the patient’s anatomic structure to conform a 3D dose distribution as precisely as possible to the tumour volume. The challenges involved in optimising CRT dose distribution range from avoiding healthy organs as much as reasonably possible and knowing the exact extent of the tumour volume to treat. The beams of CRT are delivered with uniform intensity. IMRT is a technique which uses non-uniform beam intensities to optimise 3D dose distribution across the tumour volume and minimise the dose to the surrounding normal tissue. Step and shoot IMRT generates beams with non-uniform fluence by moving the MLC within the linac for a particular beam angle. Once a beam has been delivered from several distinct MLC positions for one angle, the linac head rotates around the patient
Introduction

to the next designated beam angle. Dynamic IMRT produces beams with non-uniform fluence by continually moving the MLC within the linac for a particular beam angle while the beam is on, providing an extra degree of freedom. Intensity modulated arc therapy (IMAT) creates beams with non-uniform fluence by simultaneously rotating the linac and continuously moving the MLC leaves during treatment, thus providing another additional degree of freedom, allowing greater conformality. With greater complexity in treatment plans comes a greater need for more accurate dose calculation. Current TPSs algorithms have limitations that amplify uncertainties and these uncertainties also increase with treatment plan complexity. The most accurate method for dose calculation presently available is the Monte Carlo (MC) method.

The MC method is a simulation method used to estimate a numerical problem, in its most general form. Values are selected from within a fixed range and chosen to suit a probability distribution. The MC method models the transport of radiation particles as a random series of free flights that end with an interaction where the particle changes its direction of motion, loses energy, and in some cases, produces secondary particles. The main drawback of the MC method applied to radiation transport is that it is very computationally intensive compared to conventional analytical treatment planning algorithms. A typical time for a calculation for a TPS is of the order of a few minutes on a single machine, depending on the complexity of the treatment. MC, on the other hand, will take hours if not days. For this reasons MC is not yet routinely applicable in a clinical capacity.

MC methods have been known of for quite some time. In the 18th century, the Comte de Buffon is recognised as the first person to have employed the MC method, he applied the method to a popular parlour game at the time. He worked on calculating the probability of whether a needle tossed onto a surface would intersect a line, using a flat surface with parallel equidistant lines marked across it. The name MC comes from Monte Carlo, Monaco and was made up in the 1940s by scientists working on the Manhattan project to assign a label to the use
Introduction

of random numbers in solving problems, analogous to gambling. At some point in the development of atomic energy after World War II scientists needed to solve problems of particle transport through materials. These problems proved to be too complex to solve by hand with conventional mathematical techniques. There has since been a steady increase in the use of MC to simulate radiation transport.

With the more recent developments in RT treatment procedures, there is a growing shortfall between the accuracy and the validity of these treatments using conventional TPSs, such as Oncentra MasterPlan™ (Nucletron B.V., Veenendaal, The Netherlands) used in GUH. The McGill Monte Carlo Treatment Planning (MMCTP) (Alexander et al. 2007) System is a RT research environment which enables the comparison of MC calculated dose distributions with dose distributions generated by commercial TPS for patient specific treatment plans. MC treatment planning is seen as a solution to the shortfall in the dose calculation accuracy of present TPS dose calculation algorithms.
Introduction

Synopsis

**Biological models** introduces the mathematical framework for biological modelling in RT, specifically addressing the case of the prostate, which is fundamental to the rest of this thesis. The chapter begins with a detailed description of the mathematics of TCP modelling. A meta-analysis of clinical outcomes for intermediate risk prostate cancer and the predictions of the fitted TCP model are analysed and presented. The mathematical structure and input values of a bivariate Gaussian distributed Poisson TCP model used to predict the observed clinical outcome data is discussed. Conclusions with regard to this TCP model for these specific clinical conditions are given. The remaining portion of this chapter is given over to the description of the NTCP. The chapter concludes by combining the TCP model and the NTCP model into a single numerical indicator of treatment efficacy, the UTCP.

**Monte Carlo modelling in RT** presents the background to MC dosimetry in RT. A general explanation of MC techniques utilised to simulate the interactions of photons and electrons in matter is given, followed by a description of the specific MC applications used in this work to model radiation transport and deposition, namely BEAMnrc and DOSXYZnrc. The chapter also includes details of tuned Siemens linear accelerator models here at GUH, the method for which was developed by the medical physics research cluster (MPRC). The chapter concludes with a brief account of DICOM files, MMCTP and absolute dosimetry in MC simulations.

**Organ motion, image guidance, and dose escalation: Impact on RT** focuses on the application of the UTCP model and the MC method to a phantom study investigating the impact of organ motion, image guidance and dose escalation in RT. The phantom study examined the effect of clinically observed inter-fraction organ motion for the prostate, guided and unguided RT, as well dose
escalation, with image guidance and margin reduction, up to the dose constraints of GUH. Results for the three phantoms sizes investigated, small, medium, and large, are presented. A discussion of the phantom study along with conclusions are given.

Simulation of organ deformation in RT approaches the task of simulation of organ deformation in RT. The chapter starts with a concise description of the programming language used to write the deformation code, and a short explanation of processing DICOM-RT files. The majority of this chapter deals with the code and the various functions created to import, deform and export DICOM-RT files. A detailed description of this process is given. The chapter concludes by presenting both the original and deformed contours of a patient treated in GUH under image guidance.

Improved quantification of IGRT treatment of the prostate addresses the issues of inter-fraction organ motion, image guidance, and margin size. The chapter begins by outlining the problem of inter-fraction organ motion in RT as well as the use of PTV margins and image guidance to account for this problem. Efforts to manage and minimise the effect of organ motion are also described. A summary of treatment planning and the intra-modality US system used in GUH is given. The chapter explores the application of the UTCP, MC and organ deformation models to RT in the context of organ motion, image guidance and dose escalation limited by the dose constraints of GUH. Results for displacement statistics of inter-fraction organ motion in GUH, optimal PTV margins for inter-fraction organ motion in GUH, along with the retrospective evaluation of four prostate patients previously treated with IGRT at GUH are presented. A discussion of the improvement of IGRT along with conclusions are given.
Final conclusions and future work concludes the work presented in this thesis and discusses the implications for biological modelling, MC modelling, and treatment planning in RT. Finally, some suggestions for future related topics of research are given.
CHAPTER II

Biological models

Primarily the role of any model is to describe as precisely as possible the final result of a given process. There are several mathematical models which predict the probability of cell kill and therefore tumour control (Chadwick and Leenhouts 1973; Kellerer and Rossi 1978; Thames 1985; Curtis 1986; Brenner et al. 1998; Joiner 2004; Guerrero and Li 2004; Buckle and Lewis 2008; Park et al. 2008; Webb and Nahum 1993; Kallman et al. 1992; Ebert and Hoban 1996; Zaider and Minerbo 2000; Dasu et al. 2003; Nahum et al. 2003; Tome and Fowler 2003; Carlone et al. 2004; Levin-Plotnik et al. 2004; Zaider and Hanin 2008).

II.1 Tumour control probability

With regard to RT, the LQ model enjoys the dominant position in providing quantitative radiobiological evaluation of RT treatments (Wang et al. 2003) and is now in widespread use in both experimental and clinical radiobiology (Xiong et al. 2005). The LQ model describes the surviving fraction $S(D)$ of a population of cells irradiated by a total dose $D$, where $D$ is the total dose delivered in $n$ fractions of dose $d$, $\alpha$ and $\beta$ are the linear and quadratic coefficients respectively, characterising intrinsic radiosensitivity (Brenner et al. 1995).
The effect of simultaneous induction and repair of sublethal lesions during protracted irradiation may be modelled by multiplying the quadratic coefficient with the Lea-Catcheside function $G$ which describes this effect (Kellerer and Rossi 1978).

\[ G = \frac{2}{D^2} \int_{-\infty}^{+\infty} \hat{D}(t)dt \int_{-\infty}^{t} \hat{D}(t')e^{-\lambda(t-t')}dt' \]  

(II.2)

The biophysical interpretation of equation II.2 is that a potentially lethal lesion created at time $t'$, if not repaired, may interact in pairwise fashion with a second lesion produced at time $t$ (Brenner et al. 1998). $\hat{D}(t)$ is the dose rate as a function of the time $t$ and $\lambda$ is the repair rate constant which is related to the repair half-time $\tau$ through the expression: $\lambda = \ln(2)/\tau$. For fractionated treatment, equation II.2 reduces to (Thames 1985).

\[ G = \left( \frac{2}{m} \right) \left( \frac{\theta}{1-\theta} \right) \left( m - \frac{1 - \theta^n}{1 - \theta} \right) \]  

(II.3)

Here $m$ is the number of fractions per day, $\theta = \exp[-\tau\Delta T]$, and $\Delta T$ is the interval between fractions. For fractionated treatment equation II.1 can then be rewritten as (Jones et al. 2001).

\[ S(D) = \exp[-\alpha nd - \beta nd^2 + G \cdot d^2] \]  

(II.4)

The LQ model describes cellular radiation damage as a random event. In this model it is assumed that post irradiation, a cell will either survive with complete functionality or will be damaged beyond repair. The concept of TCP evolves from the assumption that control is only achieved if no clonogens survive (Webb et al. 1994). Here $N_0$ is the initial clonogen sum.
TCP = \exp[-N_0 S(D)] \quad \text{(II.5)}

In order to incorporate the spread of normally distributed radiosensitivity characteristics throughout a given population, a cumulative density function is required. This enables the calculation of TCP for a Gaussian distributed range of radiosensitivity parameters (Nahum et al. 2003). Thus equation II.5 is rewritten as equation II.6, the fully heterogeneous population averaged TCP model.

\[
TCP = \frac{1}{2\pi \sigma_{\alpha,\beta}^2} \int_{\alpha,\beta} \left( \exp[-N_0 S(D)] \right) \exp \left[ \frac{-(\alpha - \bar{\alpha})^2 - (\beta - \bar{\beta})^2}{2\sigma_{\alpha,\beta}^2} \right] d\alpha d\beta \quad \text{(II.6)}
\]

**Figure II.1:** The bi-variate Gaussian distribution: This is the simplest case of a bi-variate Gaussian distribution, as there is no correlation among the variables \(\alpha\) and \(\beta\), the elements of each vector are independent univariate Gaussian random variables.

The above bi-variate Gaussian distribution was used in this thesis.

Generally, the integral in equation II.6 cannot be evaluated analytically and can only be estimated through numerical methods (Webb and Nahum 1993).
\[ TCP = \left( \frac{1}{k} \right) \sum_{i=1}^{k} \left( \exp[-N_0 S(D)_k] \right) \] (II.7)

Where \( k \) represents groups of patients, each with a separate radiosensitivity.

\[ TCP \propto \exp \left[ -\left( \alpha - \bar{\alpha} \right)^2 - \left( \beta - \bar{\beta} \right)^2 \right] \frac{2 \sigma_{\alpha,\beta}^2}{2} \] (II.8)

Computationally the modelling process is carried out by selecting \( \alpha \) and \( \beta \) from independent Gaussian distributions, substituting them into equation II.4 and then summing over the range, \( k \), described by equation II.7. The sample size, \( k \), was set to \( 1 \times 10^6 \) for each Gaussian distribution, excluding negative values. Figure II.2 shows the variation in TCP at each iteration of the sample size. This large value for \( k \) ensures that the precision of the TCP model is consistent.

Figure II.2: Variation in TCP: As the sample size \( k \) increases, the percentage difference in TCP can be seen to initially decrease rapidly (1 - 1 \( \times \) 10^2) before slowly reducing further still (1 \( \times \) 10^2 - 1 \( \times \) 10^6). The inset graph shows the final values of the percentage difference in TCP fluctuate between ±0.2%. TCP in this example was calculated using equation II.7 for a standard fractionation regime of 2.0 Gy per fraction for 37 fractions.
II.2 Fitting the TCP model to tumour control clinical data

The TCP model was fitted to clinical data obtained from the literature for intermediate risk prostate patients for fractionation regimes of $1.2 - 3.1$ Gy per fraction. The clinical outcome was reported in these studies as a percentage success rate of 5 year biological no evidence of disease (bNED). Here, bNED is characterised by an absence of three consecutive rises in prostate specific antigen (PSA), in accordance with the American society for therapeutic radiology and oncology (ASTRO) definition of biochemical failure (Kuban et al. 2003) or the nadir + 2 ng/ml definition of biochemical failure (Roach et al. 2006) in accordance with the Phoenix consensus conference (PCC). Data published more than a decade ago defined intermediate risk as (pretreatment) PSA in the range $10 - 20$ ng/ml along with the restriction that the stage must not have progressed beyond T2 (Fowler et al. 2001). More precise and recent definitions include, stage T1-T2 and Gleason score of $< 7$ and PSA of $10.0 - 19.9$ ng/ml or stage T1-T2 and Gleason score of 7 and PSA of $< 20$ ng/ml (Leborgne and Fowler 2009). In the comparison reported here all definitions (both pre 2000 and more recent) were considered. The use of androgen deprivation therapy (ADT) is also indicated.

Table II.1: 5 year bNED clinical outcomes for intermediate risk prostate patients

<table>
<thead>
<tr>
<th># Patients</th>
<th>d (Gy)</th>
<th>D (Gy)</th>
<th>bNED (%)</th>
<th>Defined</th>
<th>ADT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>1.2</td>
<td>79.2</td>
<td>81</td>
<td>ASTRO</td>
<td>Yes</td>
<td>(Valdagnia et al. 2005)</td>
</tr>
<tr>
<td>116</td>
<td>1.8</td>
<td>68.4</td>
<td>54</td>
<td>ASTRO</td>
<td>No</td>
<td>(Zelefsky et al. 1998)</td>
</tr>
<tr>
<td>94</td>
<td>1.8</td>
<td>77.4</td>
<td>79</td>
<td>ASTRO</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>142</td>
<td>1.9</td>
<td>68.4</td>
<td>45</td>
<td>ASTRO</td>
<td>No</td>
<td>(Vicini et al. 1999)</td>
</tr>
<tr>
<td>16</td>
<td>1.9</td>
<td>66.5</td>
<td>50</td>
<td>ASTRO</td>
<td>No</td>
<td>(Stokes 2000)</td>
</tr>
<tr>
<td>124</td>
<td>2.0</td>
<td>66.0</td>
<td>44</td>
<td>ASTRO</td>
<td>No</td>
<td>(Pollack and Zagars 1997)</td>
</tr>
<tr>
<td>106</td>
<td>2.0</td>
<td>70.0</td>
<td>60</td>
<td>ASTRO</td>
<td>No</td>
<td>(Pollack et al. 2000)</td>
</tr>
<tr>
<td>29</td>
<td>2.0</td>
<td>78.0</td>
<td>86</td>
<td>ASTRO</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>2.1</td>
<td>71.4</td>
<td>70</td>
<td>ASTRO</td>
<td>No</td>
<td>(Hanks et al. 2000)</td>
</tr>
<tr>
<td>36</td>
<td>2.1</td>
<td>75.6</td>
<td>83</td>
<td>ASTRO</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.1</td>
<td>77.7</td>
<td>87</td>
<td>ASTRO</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.5</td>
<td>70.0</td>
<td>88</td>
<td>ASTRO</td>
<td>Yes</td>
<td>(Kupelian et al. 2005)</td>
</tr>
<tr>
<td>45</td>
<td>3.1</td>
<td>62.0</td>
<td>84</td>
<td>PCC</td>
<td>Yes</td>
<td>(Leborgne and Fowler 2009)</td>
</tr>
</tbody>
</table>
Table II.1 summarises the pertinent data.

The TCP model is analytically intractable (Webb and Nahum 1993) and therefore standard fitting techniques are not appropriate. The model was consequently fitted using the Nelder-Mead (NM) simplex algorithm (Lagarias et al. 1998). The NM simplex algorithm is a method for finding a local minimum of a function with several variables (Lee et al. 2006; Olofsson et al. 2007). For three variables, a simplex is a tetrahedron, and the method is a pattern search that compares function values at the four vertices of the simplex. The worst vertex is rejected and replaced with a new vertex. A new simplex is formed and the search is continued. The algorithm modifies the simplex repeatedly according to the following procedure until the termination test is satisfied. One iteration of the NM method consists of the following three steps.

1. Ordering: Determine the indices of the vertices from worst to best, respectively, in the current working simplex. \( f(x_{n+1}) > f(x_2) > f(x_1) > f(x_0) \) (i.e. \( x_{n+1} \) is the worst vertex)

2. Centroid: calculate the centroid, \( \bar{x} \), of the best face – this is the one opposite the worst vertex. \( \bar{x} = \frac{1}{n} \sum x_i \)

3. Transformation: Compute the new working simplex from the current one. First, try to replace only the worst vertex \( x_{n+1} \) with a better point by using reflection, expansion or contraction with respect to the best face. If this succeeds, the accepted vertex becomes part of the new working simplex. If this fails, the simplex shrinks towards the best vertex \( x_0 \). In this case, \( n \) new vertices are computed. All test vertices lie on the line defined by \( x_{n+1} \) and \( \bar{x} \).

Simplex transformations in the NM method are controlled by four parameters: \( \alpha \) for reflection, \( \beta \) for contraction, \( \gamma \) for expansion and \( \delta \) for shrinkage. The standard values are \( \alpha = 1, \beta = 1, \gamma = 2, \) and \( \delta = 1/2 \).
Biological models

Figure II.3: Nelder-Mead simplex: The NM algorithm uses a simplex of $n + 1$ vertices for $n$-dimensional vectors $x$. The algorithm initially generates a simplex around the initial guess $x_0$ by adding 5% of each component $x_0(i)$ to $x_0$, and using these $n$ vectors as elements of the simplex in addition to $x_0$.

Figure II.4: Nelder-Mead reflect: Compute the reflection point $x_r = \bar{x} + \alpha(\bar{x} - x_{n+1})$ and $f_r = f(x_r)$. If $f_0 \leq f_r < f_1$, accept $x_r$ and terminate the iteration.

Figure II.5: Nelder-Mead expand: If $f_r < f_0$, compute the expansion point $x_e = \bar{x} + \gamma(x_r - \bar{x})$ and $f_e = f(x_e)$. If $f_e < f_r$, accept $x_e$ and terminate the iteration. Otherwise if $f_e = f_r$, accept $x_r$ and terminate the iteration.

The NM simplex algorithm is a robust method for finding a local minimum of a function with several variables (Lagarias et al. 1998). To minimise the chance that the algorithm would converge to a sub-optimal local solution instead of an optimum global minimum, the algorithm was started using several initial estimates, see Table II.2. The algorithm was employed to minimise the sum of the square of errors produced by the TCP model. In order for the NM simplex algorithm to search only the radiosensitivity solution space of the clinical outcome
Figure II.6: Nelder-Mead contract: If \( f_r = f_s \), compute the contraction point \( x_c \) by using the better of the two points \( x_{n+1} \) and \( x_r \). Outside: If \( f_s = f_r < f_{n+1} \), compute \( x_c = \bar{x} + (x_r - \bar{x}) \) and \( f_c = f(x_c) \). If \( f_c = f_r \), accept \( x_c \) and terminate the iteration. Otherwise, perform a shrink transformation. Inside: If \( f_r = f_{n+1} \), compute \( x_c = \bar{x} + \beta(x_{n+1} - \bar{x}) \) and \( f_c = f(x_c) \). If \( f_c < f_{n+1} \), accept \( x_c \) and terminate the iteration. Otherwise, perform a shrink transformation.

Figure II.7: Nelder-Mead shrink: Compute \( n \) new vertices \( x_j = x_0 + \delta(x_j - x_0) \) and \( f_j = f(x_j) \), for \( j = 1, n + 1 \), with \( j \neq 0 \). This produces three new vertices by reducing the distance between the vertex \( x_0 \) and the vertices \( x_{1,2,3} \) by \( \delta \).

data set, a fixed value for the total initial clonogen sum was necessary. A clonogen is defined as a neoplastic stem cell, these cells have the capacity to maintain their numbers whilst at the same time producing cells which can differentiate and proliferate to replace the rest of the functional cell population (Steel 2002).

Numerous authors have described a concept referred to as the dominant intraprostatic lesion (DIL) to describe the area within the prostate most involved with prostate cancer (Pickett et al. 1999; van Lin et al. 2006; Pouliot et al. 2004). This concept of clonogen density distribution has been utilised in this modelling study through two discrete clonogen density values, \( \rho_{\text{prostate}} \) and \( \rho_{\text{DIL}} \), equal to
10^5 \text{ cm}^{-3} \text{ and } 10^6 \text{ cm}^{-3} \text{ respectively. These values characterise the expected clonogen density found in the regular and DIL regions of the prostate volume respectively. The ratio of clonogen density within the DIL and the regular region of the prostate is one order of magnitude. The DIL volume is assumed to be 10\% of the total prostate volume, this value is approximate to an average value calculated from prostate clonogen density distribution maps produced from six radical prostatectomy specimens (Nutting et al. 2002). The fixed value for the total initial clonogen number was produced by equation II.9.

\[ N_0 = \left( \frac{90 \rho_{\text{prostate}}}{100} + \frac{10 \rho_{DIL}}{100} \right) \text{Volume}_{\text{prostate}} \]  (II.9)

A prostate volume of 36 cm³, an average value derived from GUH clinical data for prostate tumours, was used in the calculation of equation II.9. This value is similar to other reported values for average prostate tumour volumes (Gaudet et al. 2010; DeMeerleer et al. 2000).

The effect of hypoxia in RT is considerable (Gray et al. 1953) and should therefore be incorporated into the modelling process. Previously published clinical data expresses the presence of very low values of partial pressure of oxygen (PO2) throughout the diseased portion of the prostate gland in some patients, whereas other diseased glands are well oxygenated (Movsas et al. 2000, 2002). Figure II.8 shows that circa 40\% of 115 patients had median PO2 values of \( \leq 2 \text{ mm Hg} \), and approximately 20\% were severely hypoxic with values \( \leq 1 \text{ mm Hg} \). For the bulk of tumours with median PO2 values of 1 mm Hg and less, there were little or no oxygen measurements of 10 mm Hg or higher. Furthermore, for tumours that had a median PO2 of 10 mm Hg and higher, few or no oxygen measurements of 1 mm Hg or less were measured. Accordingly, the patient population PO2 status was integrated into the model through two discrete groups. The total initial number of clonogens was composed of fully oxygenated clonogens and completely hypoxic clonogens, along with the assumption that these conditions persist throughout RT treatment (Hall 2006). According to probability theory
Biological models (Childers 1997) under the assumption that the distributions of DILs and hypoxia are independent, the proportion of the total initial number of clonogens defined as aerobic and hypoxic should be 80% and 20% respectively, based on the data shown in Figure II.8. However, a survey of all published data on hypoxic tumour fractions reported that of 42 tumour types studied, 37 were found to contain hypoxic cells in at least one study. These hypoxic fractions ranged from 0% to 50%, with a tendency for many results to average around 15% (Moulder and Rockwell 1984; Hall 2006; Wang et al. 2006). This distribution of hypoxia has also been used in previous modelling studies (Nahum et al. 2003; Wang et al. 2006), as a consequence the proportion of the total initial number of clonogens defined as aerobic and hypoxic in this modelling exercise was 85% and 15% respectively. This proportion is predicted by probability theory to be consistent in the DIL and regular regions of the prostate (Childers 1997).

![Figure II.8: Measurement of PO2 values in prostate cancer](image)

**Figure II.8:** Measurement of PO2 values in prostate cancer: A normalised distribution function of median PO2 (mm Hg) measured by microelectrodes in 115 prostate cancer patients before receiving LDR or HDR brachytherapy at the Fox Chase Cancer Center. Custom made Eppendorf PO2 microelectrodes were used to obtain PO2 measurements from the pathologically involved region of the prostate (as determined by the pretreatment sextant biopsies) as well as from a region of normal muscle for comparison. Each set of measurements comprised approximately 100 separate readings of PO2. Reproduced from (Nahum et al. 2003).
The $\alpha$ and $\beta$ parameters for radiosensitivity depend on PO2, and this dependence can be described by the oxygen enhancement ratio (OER).

$$\alpha_h = \alpha_o / \text{OER} \quad \beta_h = \beta_o / \text{OER}^2$$ (II.10)

Where, $\alpha_o$ & $\beta_o$ and $\alpha_h$ & $\beta_h$ are the radiosensitivities under oxygenated and hypoxic conditions respectively (Malinen et al. 2006). The OER as a function of the PO2 is found by fitting experimental enhancement ratios (Chapman et al. 1975; Palcic and Skarsgard 1984) to the phenomenological relation.

$$\text{OER} = \left( \frac{\text{OER}_{\text{max}} - \text{OER}_{\text{min}}}{\text{PO2} + K_m} \right) + \text{OER}_{\text{min}}$$ (II.11)

Where $\text{OER}_{\text{max}}$ and $\text{OER}_{\text{min}}$ are the maximum and minimum dose enhancement, corresponding to minimum and maximum oxygen levels respectively. $K_m$ is the PO2 where half-maximum sensitisation is obtained, $K_m$ is fixed. The parameters describing the dose modifying effects of oxygen have previously been reported (Chapman et al. 1975; Palcic and Skarsgard 1984; Wouters and Brown 1997; Nahum et al. 2003; Malinen et al. 2006), a typical value for the OER is 1.75.

Here the OER produces a purely dose modifying effect, i.e. the magnitude of the overall OER does not change with dose per fraction. This is reasonable when a constant dose per fraction is maintained throughout RT treatment (Dale 2007). Thus equation II.4 may be rewritten, in order to incorporate hypoxia into the modelling process.

$$S_h(D) = \exp \left[ -\alpha_h n d - \beta_h n (1 + G) d^2 \right]$$ (II.12)

Equations II.4 and II.12 were applied accordingly to the fractions of the total initial number of clonogens defined as aerobic and hypoxic.
Biological models

Residuals and goodness of fit statistics, weighted to avoid bias, were employed to assess the accuracy of the fitted TCP model. The TCP model, using the biological input parameters listed in Table II.3, was subsequently used to predict the clinical outcome of very large fractionation regimes, as utilised in stereotactic body radiotherapy (SBRT), 9.0, 9.5, and 10.0 Gy per fraction in this instance. These predictions were then compared with clinical outcome data, 2.5 year bNED, reported for SBRT (Boike et al. 2011).

The residual for a specific predictor value is the difference between the specific clinical outcome \( y_i \) and the specific predicted TCP value \( x_i \).

\[
r_i = y_i - x_i
\]

The sum of squares due to error measures the total deviation of the TCP values from the fit to the clinical outcomes. This deviation was weighted to the number of patients treated in each data point so as to avoid bias within the data set.

\[
SSE = \sum_{i=1}^{n} w_i (y_i - x_i)^2
\]

The total sum of squares is a measure of the variance in a data set.

\[
SST = \sum_{i=1}^{n} w_i (y_i - \bar{y})^2
\]

R-squared describes the square of the correlation between the clinical outcomes and the TCP values.

\[
R^2 = 1 - \frac{SSE}{SST}
\]

The root mean squared error is an estimate of the standard deviation of the random component in the residual data, and is defined as.
\[ \text{RMSE} = \sqrt{\frac{\text{SSE}}{n - 1}} \]  \hspace{1cm} (II.17)

Where \( n \) is the number of clinical observations.

A two sample t-test of the null hypothesis that data in the TCP and clinical outcome vectors, \( x \) and \( y \), are independent random samples from normal distributions with equal means and equal but unknown variances, against the alternative that the means are not equal, was performed. The p-value is the probability, under the null hypothesis, of observing a value as extreme or more extreme than the test statistic, \( t \).

\[ t = \frac{\bar{x} - \bar{y}}{\sqrt{\frac{s^2}{n}}} \]  \hspace{1cm} (II.18)

Here \( s \) is the pooled standard deviation. The test is performed under the assumption of equal population variances, and computes a pooled sample standard deviation using.

\[ s = \sqrt{\frac{(n - 1)(s_x^2 + s_y^2)}{2n - 2}} \]  \hspace{1cm} (II.19)

Where \( s_x \) and \( s_y \) are the standard deviations of \( x \) and \( y \), respectively.

II.3 Results of the TCP model analysis

Table II.2 displays the initial guesses for the biological input parameters of the TCP model, along with several local minimum solutions and the global minimum solution produced by the NM simplex algorithm from the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data. The NM
simplex algorithm was employed to minimise the sum of the square of errors produced by the TCP model. The optimum global minimum solution, the lowest RMSE and highest $R^2$ value, is highlighted in grey in rows 10 and 11. Table II.3 lists the biological input parameters for the TCP model, produced by the NM simplex algorithm from the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data. Table II.3 also lists the range for these values reported in the literature (Carlson et al. 2004; Nahum et al. 2003; Dasu 2007; Valdagnia et al. 2005).

<table>
<thead>
<tr>
<th>Table II.2: Input parameters optimisation for the TCP model</th>
<th>Initial Guess</th>
<th>$R^2$</th>
<th>RMSE</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\bar{\alpha}, \bar{\alpha}/\beta, \sigma_{\alpha,\beta}]$</td>
<td>[0.10, 10.0, 0.010]</td>
<td>-12.43</td>
<td>18.11</td>
<td>[0.10, 10.0, 0.010]</td>
</tr>
<tr>
<td>2</td>
<td>[0.10, 2.0, 0.010]</td>
<td>-12.43</td>
<td>18.11</td>
<td>[0.10, 2.0, 0.010]</td>
</tr>
<tr>
<td>3</td>
<td>[0.25, 10.0, 0.025]</td>
<td>0.92</td>
<td>1.41</td>
<td>[0.24, 2.06, 0.026]</td>
</tr>
<tr>
<td>4</td>
<td>[0.25, 2.0, 0.025]</td>
<td>0.92</td>
<td>1.43</td>
<td>[0.24, 1.96, 0.027]</td>
</tr>
<tr>
<td>5</td>
<td>[0.50, 10.0, 0.050]</td>
<td>0.54</td>
<td>3.37</td>
<td>[0.35, 6.33, 0.059]</td>
</tr>
<tr>
<td>6</td>
<td>[0.50, 2.0, 0.050]</td>
<td>0.63</td>
<td>3.00</td>
<td>[0.16, 0.71, 0.077]</td>
</tr>
<tr>
<td>7</td>
<td>[0.10, 10.0, 0.020]</td>
<td>0.41</td>
<td>3.78</td>
<td>[0.38, 53.57, 0.030]</td>
</tr>
<tr>
<td>8</td>
<td>[0.10, 2.0, 0.020]</td>
<td>0.92</td>
<td>1.40</td>
<td>[0.23, 1.95, 0.026]</td>
</tr>
<tr>
<td>9</td>
<td>[0.25, 10.0, 0.050]</td>
<td>0.82</td>
<td>2.08</td>
<td>[0.29, 4.01, 0.002]</td>
</tr>
<tr>
<td>10</td>
<td>[0.25, 2.0, 0.050]</td>
<td>0.92</td>
<td>1.39</td>
<td>[0.24, 2.06, 0.025]</td>
</tr>
<tr>
<td>11</td>
<td>[0.50, 10.0, 0.100]</td>
<td>0.92</td>
<td>1.39</td>
<td>[0.24, 2.06, 0.025]</td>
</tr>
<tr>
<td>12</td>
<td>[0.50, 2.0, 0.100]</td>
<td>0.91</td>
<td>1.46</td>
<td>[0.24, 2.28, 0.021]</td>
</tr>
</tbody>
</table>

Figures II.9 and II.10 show the radiosensitivity solution space of the TCP model computed from the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data. Figure II.15 shows the residuals of the TCP model computed from the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, along with SBRT clinical outcome data.

<table>
<thead>
<tr>
<th>Table II.3: TCP model input parameters and previously reported range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{\alpha}$</td>
</tr>
<tr>
<td>(Gy$^{-1}$)</td>
</tr>
<tr>
<td>TCP</td>
</tr>
<tr>
<td>CI 95%</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>
Figure II.9: Radiosensitivity solution space: A surface of the radiosensitivity solution space is shown here for a value of $\sigma_{\alpha,\beta}$ set to 10.4%. The optimal global minimum solution, the smallest RMSE, is found at $\bar{\alpha} = 0.24 \text{ Gy}^{-1}$ and $\bar{\alpha}/\bar{\beta} = 2.06 \text{ Gy}$.

Figure II.10: Radiosensitivity solution space: A surface of the radiosensitivity solution space is shown here for a value of $\sigma_{\alpha,\beta}$ set to 10.4%. The optimal global minimum solution, the highest $R^2$, is found at $\bar{\alpha} = 0.24 \text{ Gy}^{-1}$ and $\bar{\alpha}/\bar{\beta} = 2.06 \text{ Gy}$. 
In order to quantitatively assess the validity of the TCP model, residuals analysis and weighted goodness of fit statistics were applied. Figure II.15 displays the residuals produced by the TCP model when compared with the 5 year bNED clinical outcome data for hyper, standard, and hypo-fractionated treatments, together with SBRT clinical outcome data. A statistical analysis of the models’ predictions, judged against the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, resulted in an $R^2$ value of 0.92 and a RMSE of 1.39%. Figures II.11 - II.13 display the TCP curves for hyper, standard, and hypo-fractionated treatment with 5 year bNED clinical outcome data. Figure II.14 displays the TCP curves for SBRT treatment with 2.5 year bNED clinical outcome data. The accuracy of the TCP model’s prediction is clearly evident when compared with the SBRT 2.5 year bNED clinical outcome data. Residuals of 2.0%, 0.9% and 0.4% are respectively produced by the TCP model when compared against the 2.5 year bNED clinical outcome data for SBRT. The capacity of the TCP model to accurately extrapolate from hyper, standard, and hypo-fractionated treatments to SBRT treatments is indicative of a sound radiobiological mechanistic construct. The result of the t-test returned indicates a failure to reject the null hypothesis at the 5% significance level. $p = 0.99$ with confidence intervals = (-13.7, 13.5). This result provides further support for the incorporation of normally distributed radiosensitivity parameters in the model.

**Table II.4: Clinical outcomes compared with TCP model predictions**

<table>
<thead>
<tr>
<th># Patients</th>
<th>d (Gy)</th>
<th>D (Gy)</th>
<th>bNED (%)</th>
<th>TCP (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>1.2</td>
<td>79.2</td>
<td>81</td>
<td>77</td>
<td>(Valdagnia et al. 2005)</td>
</tr>
<tr>
<td>116</td>
<td>1.8</td>
<td>68.4</td>
<td>54</td>
<td>47</td>
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<td>94</td>
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<td>79</td>
<td>80</td>
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<td>16</td>
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<tr>
<td>124</td>
<td>2.0</td>
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<td>(Pollack and Zagars 1997)</td>
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<td>106</td>
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<td>60</td>
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<tr>
<td>29</td>
<td>2.0</td>
<td>78.0</td>
<td>86</td>
<td>87</td>
<td></td>
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<tr>
<td>42</td>
<td>2.1</td>
<td>71.4</td>
<td>70</td>
<td>74</td>
<td>(Hanks et al. 2000)</td>
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<tr>
<td>36</td>
<td>2.1</td>
<td>75.6</td>
<td>83</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.1</td>
<td>77.7</td>
<td>87</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.5</td>
<td>70.0</td>
<td>88</td>
<td>83</td>
<td>(Kupelian et al. 2005)</td>
</tr>
<tr>
<td>45</td>
<td>3.1</td>
<td>62.0</td>
<td>84</td>
<td>82</td>
<td>(Leborgne and Fowler 2009)</td>
</tr>
</tbody>
</table>
Biological models

**Figure II.11:** TCP curves and 5 year bNED clinical outcome data for hyper-fractionation: The black circle depicts the 5 year bNED clinical outcome reported for hyper-fractionation, among typical errors of $\pm4.1\%$ uncertainty in the dose delivered (Ahnesjo and Aspradakis 1999) with vertical Poisson error bars (Nahum et al. 2003), delivered in fractions of 1.2 Gy. The blue curve represents the TCP model with optimised biological input parameters listed in Table II.3. Hyper-fractionation refers to 2 treatments per day for 5 days of the week. Hyper-fractionation has a $\Delta T$ value of 7 hrs. ADT used in approximately 71% of patients. bNED defined by ASTRO.

**Figure II.12:** TCP curves and 5 year bNED clinical outcome data for hypo-fractionation: The black circles depict the 5 year bNED clinical outcome reported for hypo-fractionation, among typical errors of $\pm4.1\%$ uncertainty in the dose delivered (Ahnesjo and Aspradakis 1999) with vertical Poisson error bars (Nahum et al. 2003), delivered in fractions of 2.5 and 3.1 Gy. The blue curves represent the TCP model with optimised biological input parameters listed in Table II.3. Hypo-fractionation refers to 1 treatment per day for 4 days of the week. Hypo-fractionation has a $\Delta T$ value of 24 hrs. ADT used in approximately 53% and 33% of the patients in the 2.5 and 3.1 Gy hypo-fractionation treatment groups respectfully. bNED defined by ASTRO and PCC for the 2.5 and 3.1 Gy hypo-fractionation treatment groups respectfully.
Biological models

Figure II.13: TCP curves and 5 year bNED clinical outcome data for standard-fractionation: The black circles depict the 5 year bNED clinical outcome reported for standard-fractionation, among typical errors of ±4.1% uncertainty in the dose delivered (Ahnesjo and Aspradakis 1999) with vertical Poisson error bars (Nahum et al. 2003), delivered in fractions of 1.8, 1.9, 2.0 and 2.1 Gy. The blue curves represent the TCP model with optimised biological input parameters listed in Table II.3. Standard-fractionation refers to 1 treatment per day for 5 days of the week. Standard-fractionation has a ΔT value of 24 hrs. bNED defined by ASTRO.
Figure II.14: TCP curves and 2.5 year bNED clinical outcome data for SBRT: The black circles depict the 2.5 year bNED clinical outcome reported for SBRT, among typical errors of $\pm 4.1\%$ uncertainty in the dose delivered (Ahnesjo and Aspradakis 1999) with vertical Poisson error bars (Nahum et al. 2003), delivered in fractions of 9.0, 9.5 and 10.0 Gy. The blue curves represent the TCP model with optimised biological input parameters listed in Table II.3. SBRT refers to 5 treatments over 2 weeks. SBRT has a $\Delta T$ value of 24 hrs. bNED defined by PCC.
Biological models

Figure II.15: Residuals for hyper, standard, hypo-fractionated, and SBRT treatments: The graph is split in two by the region control line (black vertical dashed line). To the right of the region control line is the fitting region, here the 5 year bNED clinical outcomes for hyper, standard, and hypo-fractionated (red diamond solid line) treatments, fractionation regimes of 1.2-3.1 Gy per fraction, were used to produce radiobiological parameters, see Table II.3 using the NM simplex algorithm. To the left of the region control line is the extrapolation region, here the mechanistic quality of the TCP model is tested against SBRT treatments. The TCP model successfully predicts the 2.5 year bNED clinical outcome reported for SBRT (red triangle dashed line) as well as the projected 5 year bNED clinical outcome for SBRT (red circle dashed line), delivered in fractions of 9.0, 9.5 and 10.0 Gy. The TCP model calculates the 5 year bNED clinical outcomes for hyper, standard, and hypo-fractionated treatments with a high degree of accuracy. The lack of a distinct pattern in the scatter of the residuals indicates a low likelihood of systemic error in the model. Hypo-fractionation refers to 1 treatment per day for 4 days of the week. Standard-fractionation refers to 1 treatment per day for 5 days of the week. Hyper-fractionation refers to 2 treatments per day for 5 days of the week. Hypo-fractionation and Standard-fractionation both have a \( \Delta T \) value of 24 hrs, Hyper-fractionation has a \( \Delta T \) value of 7 hrs. SBRT refers to 5 treatment over 2 weeks with a \( \Delta T \) value of 24 hrs. A statistical analysis of the models’ predictions, judged against the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, resulted in an \( R^2 \) value of 0.92 and a RMSE of 1.39\%.
Figure II.16: Linear regression for hyper, standard, and hypo-fractionated treatments: The analysis show a high degree of correlation between the predicted TCP outcomes and the observed 5 year bNED clinical outcomes, providing a measure of confidence in the accuracy of the TCP model to predict clinical outcomes across a wide variety of treatment scenarios. A statistical analysis of the models’ predictions, judged against the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, resulted in an $R^2$ value of 0.92 and a RMSE of 1.39%.

II.4 Discussion of the TCP models

Radiobiology has progressed sufficiently to provide us with a suitable understanding of the radiation response of a wide spectrum of cell lines (Carlson et al. 2004; Nahum et al. 2003), and this knowledge supplies a degree of certainty in our ability to describe this radiation response using mathematical models (Carlone et al. 2003). A natural extension of this knowledge is to use it in RT to help predict the expected tumour control. A meta-analysis of $\alpha$ and $\beta$ coefficients reported
for asynchronous populations of human prostate cancer cell lines is presented in Table II.5 (Nahum et al. 2003).

<table>
<thead>
<tr>
<th>Cell line</th>
<th>$\bar{\alpha}$ (Gy$^{-1}$)</th>
<th>$\bar{\beta}$ (Gy$^{-2}$)</th>
<th>$\bar{\alpha}/\bar{\beta}$ (Gy)</th>
<th>SF2</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSU</td>
<td>0.06</td>
<td>0.05</td>
<td>1.24</td>
<td>0.7</td>
<td>(Algan et al. 1996)</td>
</tr>
<tr>
<td>TSU-Pr1</td>
<td>0.115</td>
<td>0.015</td>
<td>7.66</td>
<td>0.62</td>
<td>(DeWeese et al. 1998)</td>
</tr>
<tr>
<td>PC-3</td>
<td>0.064</td>
<td>0.017</td>
<td>3.76</td>
<td>0.71</td>
<td>(DeWeese et al. 1998)</td>
</tr>
<tr>
<td>PC-3</td>
<td>0.24</td>
<td>0.069</td>
<td>3.48</td>
<td>0.48</td>
<td>(Algan et al. 1996)</td>
</tr>
<tr>
<td>PC-3</td>
<td>0.521</td>
<td>0.055</td>
<td>9.47</td>
<td>0.32</td>
<td>(Leith et al. 1993)</td>
</tr>
<tr>
<td>PPC-1</td>
<td>0.1</td>
<td>0.026</td>
<td>3.84</td>
<td>0.56</td>
<td>(DeWeese et al. 1998)</td>
</tr>
<tr>
<td>DU-145</td>
<td>0.099</td>
<td>0.009</td>
<td>11.00</td>
<td>0.63</td>
<td>(DeWeese et al. 1998)</td>
</tr>
<tr>
<td>DU-145</td>
<td>0.31</td>
<td>0.048</td>
<td>6.45</td>
<td>0.48</td>
<td>(Algan et al. 1996)</td>
</tr>
<tr>
<td>DU-145</td>
<td>0.155</td>
<td>0.0521</td>
<td>2.98</td>
<td>0.60</td>
<td>(Leith et al. 1993)</td>
</tr>
<tr>
<td>LnCap</td>
<td>0.68</td>
<td>0.0053</td>
<td>128</td>
<td>0.25</td>
<td>(Leith 1994)</td>
</tr>
<tr>
<td>LnCap</td>
<td>0.29</td>
<td>0.013</td>
<td>22.3</td>
<td>0.27</td>
<td>(DeWeese et al. 1998)</td>
</tr>
<tr>
<td>LnCap</td>
<td>0.49</td>
<td>0.0144</td>
<td>34.0</td>
<td>0.25</td>
<td>(Chapman 2003)</td>
</tr>
</tbody>
</table>

The asynchronous populations of tumour cells reported in Table II.5 are mixtures of cells with extensively dissimilar intrinsic radiosensitivities and consequently the $\alpha$ and $\beta$ values reported are complex averages of the parameters of several sub-populations. Some of the studies in Table II.5 reported survival data for high dose rate (HDR) experiments while others reported survival data for both low dose rate (LDR) and HDR experiments. Additionally none of these studies attempted to correct for dose rate effects when analysing the measured data. Finally all experiments were conducted in in vitro environments with varying levels of oxygenation. Survival data for several doses and dose rates and/or fractionated doses are required to determine accurate estimates of the radiosensitivity parameters $\alpha$ and $\beta$ (Carlson et al. 2004). A vital aspect of tumour cell kill due to irradiation is that there is no evidence for the repair of damage associated with the radiosensitivity parameter $\alpha$, therefore the dose rate has no effect on the $\alpha$ radiosensitivity parameter. Furthermore, $\alpha$ is less sensitive to oxygenated in vitro environments. Under these conditions, the $\alpha$ value for radiosensitivity reported in Table II.5 is
the most reliable value. This average value for $\alpha$ in Table II.5 is similar to the $\bar{\alpha}$ value in Table II.3, obtained from the NM simplex algorithm’s search of the radiosensitivity solution space of the clinical outcome data set.

Figure II.17: Ranges of $\alpha/\beta$ values for the prostate: $\alpha/\beta$ ratios for prostate carcinomas determined from iso-effect comparisons of clinical results. The dashed line represents the average $\alpha/\beta$ value (1.9 Gy) obtained when the individual points are weighted inversely proportional to the width of the stated confidence interval. In spite of several confounding factors that interfere with the derivation of a precise value, it seems that most data support a trend towards lower $\alpha/\beta$ values for prostate tumours than the 3 Gy commonly assumed for the rectum or bladder. Reproduced from (Dasu 2007).

Figure II.17 depicts a review of the clinical and experimental data regarding the radiobiological differential that might exist between prostate tumours and the late normal tissues surrounding the prostate. This review suggested that the $\alpha/\beta$ ratio that characterises the fractionation response of the prostate is low (below the 3 Gy commonly assumed for most late complications) (Dasu 2007). Figure II.17 shows the $\alpha/\beta$ ratios for prostate cancer determined from iso-effect comparisons of clinical results to be 1.9 Gy. This average value for $\alpha/\beta$ is similar to the $\bar{\alpha}/\bar{\beta}$ value in Table II.3, obtained from the NM simplex algorithms search of the radiosensitivity solution space of the clinical outcome data set.
Biological models

The debate regarding the most appropriate $\alpha/\beta$ ratio for prostate cancer (Brenner and Hall 1999; Fowler et al. 2003; Wang et al. 2003; Kal and van Gellekom 2003; Nahum et al. 2003; Valdagnia et al. 2005) is a classic example of the challenges associated with radiobiological modelling. Previously it has been assumed that prostate tumours have high $\alpha/\beta$ values, similar to most other tumours and early reacting normal tissues. However, the proliferation rate of prostate tumours is more like that of late reacting tissues, with slow doubling times and low $\alpha/\beta$ values. Therefore repopulation in the model was omitted on the grounds that the model did not need a repopulation factor to contribute to the fit of the model to any of the clinical data observed. This is in line with the conventional view of prostate cancer being a slowly proliferating cancer with a long delay before the onset of growth (Fowler et al. 2003; Wyatt et al. 2003; Yang and Xing 2005).

“As in so much of modelling, the devil is in the details” (Fowler et al. 2003). The problem is the choice of modelling parameters. While the values obtained from in vitro work are useful, there are reservations with parameters determined from cell cultures in vitro as tumours in vivo exist and proliferate in an environment different from those in vitro (Carlone et al. 2003). These reservations have lead authors to therefore use TCP curves in order to derive the necessary parameters for the modelling process. However in the past, the biological significance of these derived parameters was largely ignored, e.g. ($\alpha = 0.036 \text{ Gy}^{-1}$, $N_0 = 95$) (Brenner and Hall 1999), ($\alpha = 0.039 \text{ Gy}^{-1}$, $N_0 = 293$) (Fowler et al. 2001). Subsequent studies have since demonstrated that the use of single value parameters to explain observed clinical TCP curves is unwise (Dasu et al. 2003), and that is it therefore vital to include some distribution of input parameters within a model (Xiong et al. 2005). Evidence supporting the position that components of radiosensitivity are normally distributed amidst the populous, is provided in theory through the central limit theorem (Kallenberg 1997) and has been provided empirically (West et al. 1995). This study investigated the intrinsic radiosensitivity of tumour biopsies from patients with cervical carcinoma. Radiosensitivity was assessed for
145 tumours *in vitro* as surviving fraction at 2 Gy (SF2) using a clonogenic assay. This distribution was seen to be normal.

The distribution of SF2 values for cervical carcinoma

![Graph showing distribution of SF2 values for cervical carcinoma.](image)

**Figure II.18:** Measurement of cervical tumour surviving fraction at 2 Gy: Primary tumours were grown in culture using a modified Courtenay-Mills soft agar clonogenic assay. Intrinsic radiosensitivity was assessed as cell survival following a single *in vitro* 2 Gy dose of radiation (surviving fraction at 2 Gy). Irradiations were carried out prior to plating at room temperature using a $^{137}$Cs source with a dose rate of 3.8-4.2 Gy/min. The histogram reveals this data to be approximately Gaussian, passing the Shapiro-Wilk test for Normality: $P = 0.27$, $W$ Statistic = 0.90, at a significance level = 0.05. Reproduced from (West et al. 1995).

There is no evidence to suggest that this is not also the case for prostate carcinoma. The nature of this distribution is currently an unanswered question with regard to TCP modelling, should the radiosensitivity characteristics be distributed dependently and therefore partially heterogeneous or independently and therefore fully heterogeneous. There are a number of logical arguments which support the use of a fully heterogeneous population averaged TCP model as opposed to a partially heterogeneous population averaged TCP model. The use of full heterogeneity in TCP modelling can be made on the basis that:

- $\alpha$ and $\beta$ describe very different types of cell inactivation. $\alpha$ describes cell inactivation from small scale deletions or insertions at the nanometer level,
while $\beta$ describes exchange type chromosome aberration formation at the micrometer level (Brenner and Hall 2000).

- Escalation of the fractional dose diminishes the probability that cells will undergo repairable sublethal damage described by $\beta$. This is a consequence of the high level of energy deposited into the cells which causes irreparable damage. Hence, damage associated with $\beta$ decreases, resulting in an increase in the $\alpha/\beta$ ratio, this lead to a straightening of the survival curve. A fully heterogeneous TCP model continuously alters the $\alpha/\beta$ ratio and thus produces a cell survival curve which straightens at high fractional doses, as seen in SBRT. A partially heterogeneous TCP model with a constant $\alpha/\beta$ ratio deviates more and more from the fully heterogeneous TCP model for these large fractional doses, resulting in a grossly exaggerated overestimation of cell kill by the partially heterogeneous TCP model (Tome 2008).

![Comparison of cell survival curves having a constant and a continuously changing $\alpha/\beta$ ratio](image)

**Figure II.19:** Comparison of cell survival curves having a constant and a continuously changing $\alpha/\beta$ ratio: Cell survival curves with a continuously changing ratio $\alpha/\beta$ (black curve) become straighter as the $\beta$ component of radiosensitivity describing sub-lethal damage diminishes, deviating more and more as the dose increases from the standard LQ model (coloured curves) with constant $\alpha/\beta$ ratios.

The TCP model was fitted to 5 year bNED clinical outcome data. The SBRT clinical outcome data is for 2.5 year bNED and was therefore excluded from the
fitting procedure. Using Kaplan-Meier bNED curves for standard-fractionation and hypo-fractionation intermediate risk patients obtained from the literature (Pollack and Zagars 1997; Pollack et al. 2000; Hanks et al. 2000; Kupelian et al. 2005; Leborgne and Fowler 2009), a weighted analysis of the deterioration in bNED from 2.5 years to 5 years was calculated to be a minimum of 0%, a maximum of 5% and a mean of 3.1%. Hyper-fractionation Kaplan-Meier bNED curves were excluded on the grounds that they do not characterise the radiobiology of SBRT. This potential 3.1% reduction in the bNED reported for the SBRT clinical outcome data would diminish the accuracy of the TCP model, producing new residuals of $-1.0\%$, $-2.3\%$ and $-2.8\%$ respectively for the TCP model. The SBRT clinical outcome data will shortly mature to 5 year bNED, this will definitively clarify the absolute accuracy of the TCP model with regard to SBRT.

With regard to the initial guess for the total initial clonogen number, the assumption that clonogen density is uniformly distributed has been called into question with improvements in non-invasive prostate imaging modalities such as dynamic magnetic resonance imaging (Padhani 1999), magnetic resonance spectroscopy (Kurhanewicz et al. 1996) and functional imaging (Ling et al. 2000). Prostate tumours typically arise in the peripheral zone of the prostate gland and are commonly multifocal (Nutting et al. 2002). Histological examination of radical prostatectomy specimens frequently reveals a single large DIL within the prostate (Pickett et al. 1999). Further improvements in imaging modalities promise the ability to identify these DIL regions within the prostate gland that could be specifically targeted to receive higher doses of radiation through IMRT or other treatment modalities. In order to calculate the total initial clonogen number several studies have used the target volume along with a value of $10^7$ cm$^{-3}$ for clonogen density uniformly distributed (DeMeerleer et al. 2000; Nahum et al. 2003; Webb and Nahum 1993). Given that realistic estimates of the density of clonogens in human tumours lie in the range $10^5$-$10^7$ cm$^{-3}$ (Nahum et al. 2003), with a best estimate of $10^5$ (Baker and Sanger 1991). Using the target volume along with a value of $10^7$ cm$^{-3}$ for clonogen density uniformly distributed is a
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flawed approach and leads to an inflated estimate of the total initial clonogen number which in turn leads to an inflated estimate of radiosensitivity. Equation II.9 attempts to overcome this deficiency in the estimation of total initial clonogen number, clonogen density and clonogen distribution.

Figure II.20: Variation of TCP with tumour volume and PO2: The variation of TCP with tumour volume for four distinct PO2 values is shown. TCP was calculated for a total dose of 74 Gy delivered in 37 fractions using the biological input parameters listed in Table II.3. A modest relationship is shown to exist between the tumour volume, and therefore total clonogen number, and TCP. Conversely, the data clearly demonstrates that the relationship between TCP and PO2 status dominates.

Figure II.20 depicts the relationship between clonogen number and dose, as well as the vital role that PO2 plays in determining TCP. The results obtained in this modelling exercise are partially based on the data shown in Figure II.8. This data shows the existence of hypoxia in human prostate tumours (Movsas et al. 2000, 2002). However, there are limitations in the data that may potentially compromise the accuracy of the radiosensitivity values listed in Table II.3.
• The PO2 measurement with Eppendorf microelectrodes is a sampling method which measures only a sampled segment of the prostate. It may not perfectly depict the overall PO2 distribution in the entire tumour.

• The method fails to discriminate cell type and viability, i.e. regular and DIL regions of the prostate volume.

• The method cannot differentiate types of hypoxia: chronic and transient. Transient hypoxia may be diminished or eliminated by reoxygenation.

The radiosensitivity values listed in Table II.3 were optimised based on an average hypoxic fraction of 15%. A ±5% change in this value results in a change of ±0.1 Gy\(^{-1}\) in \(\bar{\alpha}\), ±0.1 Gy in \(\bar{\alpha}/\bar{\beta}\), and ±0.5% in \(\sigma_{\alpha,\beta}\). This provides further confidence in the optimised radiosensitivity values listed in Table II.3.

In this study we assume that the OER keeps constant for all the RT treatment fractions modelled (Dale 2007). The use of alternative models, which include temporal variations in the hypoxic fraction, might lead to quite different results. Therefore, the results obtained in this study may be limited by the approximations used in the models and the uncertainties shown in the clinical data.

With regard to the bNED data obtained from the literature, two distinct definitions of bNED, the ASTRO and PCC definitions, were used to fit the TCP model. In 1996 ASTRO sponsored a consensus conference to establish a definition of biochemical failure after RT. The ASTRO definition was not linked to clinical progression or survival; it performed poorly in patients undergoing ADT. The goal of ADT is to reduce levels of male hormones in the body, or to prevent them from reaching prostate clonogens. Lowering the level of male hormones or stopping them from getting into prostate clonogens often makes prostate cancers regress (Gregory et al. 2001). A second consensus conference was sponsored by ASTRO and the RTOG in Phoenix, Arizona in 2005 in order to revise the ASTRO definition. The panel recommended that a rise by 2 ng/ml or more above
the nadir PSA be considered the standard definition for biochemical failure after RT, with or without ADT. The panel also recommended that investigators be allowed to use the ASTRO consensus definition after RT alone (no ADT). Retaining the ASTRO definition would allow comparisons with a large existing body of literature (Roach et al. 2006). A single data point, published post-2005, in the fitted clinical outcome data set used the PCC definition of biochemical failure.

Three of the data points (Valdagnia et al. 2005; Kupelian et al. 2005; Leborgne and Fowler 2009) included ADT in approximately 71%, 53% and 33% of their patients respectively. The use of ADT can potentially be a confounding factor; however, a Cox multivariate analysis showed that the bNED in two of these data points (Valdagnia et al. 2005; Leborgne and Fowler 2009) did not correlate significantly with ADT vs. no ADT. No impact was observed from the use of ADT in the remaining data point (Kupelian et al. 2005). Thus the integrity of the model fit was not compromised.

All of the optimised radiosensitivity values listed in Table II.3 produced by the NM simplex algorithm are biologically plausible with tight confidence intervals. These values are in good agreement with both experimental and clinical observations reported in the literature through meta-analysis (Nahum et al. 2003; Dasu 2007), falling well within the bounds of the previously reported ranges (Carlson et al. 2004; Nahum et al. 2003; Dasu 2007; Valdagnia et al. 2005).
II.5 Conclusions for the TCP model

Previous studies have presented TCP models fitted to clinical outcome data. While they are appropriate for the reproduction of the curve from which they were derived, problems arise when using the same parameters to extrapolate to situations that have some changes compared to the reference conditions, i.e. the fractionation scheme for which the parameters have been derived. The focus of this study was to examine the ability of a mechanistic TCP model, using radiobiologically sound input parameters, to accurately predict treatment outcomes for a wide range of treatment strategies. This TCP model for external beam treatment of intermediate risk prostate cancer has been demonstrated to accurately forecast the 5 year bNED clinical outcomes of hypo-fractionation, standard-fractionation, and hyper-fractionation RT using the optimised radiosensitivity values listed in Table II.3 produced by the NM simplex algorithm. A statistical analysis of the TCP models’ predictions, measured against the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, resulted in an $R^2$ value of 0.92 and a RMSE of 1.39%. In addition, this TCP model using the optimised radiosensitivity values listed in Table II.3 has been demonstrated to be likely to correctly predict the 5 year bNED clinical outcomes of SBRT. The average value for $\alpha$ in Table II.5 is similar to the $\bar{\alpha}$ value in Table II.3, and the average value for $\alpha/\beta$ shown in Figure II.17 is similar to the $\bar{\alpha}/\bar{\beta}$ value in Table II.3. Both these values listed in Table II.3 were obtained by the NM simplex algorithm’s search of the radiosensitivity solution space of the 5 year bNED clinical outcome data set for hyper, standard, and hypo-fractionated RT treatments. These values were obtained through a robust fitting procedure using the NM simplex algorithm based upon the best available clinical data for dose response, total initial clonogen number, clonogen density, clonogen distribution, and hypoxia status of the average in intermediate risk prostate cancer patient. These results along with the theoretical and experimental radiobiological merit of this TCP model, lead to the conclusion that this TCP model used with the optimised radiosensitivity values listed in Table II.3 obtained by the NM simplex
algorithm’s search of the radiosensitivity solution space of the 5 year bNED clinical outcome data set for hyper, standard, and hypo-fractionated RT treatments, is appropriate for the analysis and evaluation of external beam RT plans with regard to tumour control for a wide variety of RT treatment scenarios under these clinical conditions.

II.6 Normal tissue complication probability

Similar to mathematical descriptions which calculate tumour control, it is also possible to calculate damage to normal tissue. NTCP can be determined through equation II.21, also known as the Lyman-Kutcher-Burman (LKB) NTCP model. In order to bridge the gap between uniform irradiation and partial irradiation, the equivalent uniform dose (EUD) was devised (Kutcher et al. 1991). The EUD describes the dose that yields an equivalent survival fraction as a heterogeneous dose distribution, if delivered uniformly to the entire volume of a structure. The phenomenological, generalised EUD (gEUD) formalism, for OARs is postulated as follows (Niemierko 1997).

\[
gEUD = \left( \frac{1}{N} \sum_{i=1}^{N} (D_i)^a \right)^{\frac{1}{a}} \tag{II.20}
\]

Where \(N\) is the number of voxels in the structure of interest, \(D_i\) the total dose in the \(i\)th voxel, and \(a\) is the phenomenological model parameter that describes the magnitude of the volume effect (Chvetsov et al. 2007). Based upon the gEUD metric, the response of OARs for a given RT regime can be described by the following model (Lyman 1985).

\[
NTCP = \frac{1}{\sqrt{2\pi}} \int_{0}^{t} e^{-\frac{x^2}{2}} dx \tag{II.21}
\]

where
Here $TD_{50}$ is the uniform dose given to the entire OAR which results in a 50% risk of complication, $m$ is a measure of the slope of the sigmoid curve represented by the integral of the normal distribution (Stewart and Li 2007).

The volume effect represents the architecture of OARs, which are assumed to consist of independent functional sub units (FSUs) (Withers et al. 1988), arranged in series, parallel, or some combination of the two as illustrated in Figure II.21. The volume effect plays an important role in the response of an OAR. When $\frac{1}{a}$ is near unity the volume effect is large and when $\frac{1}{a}$ is near 0 the volume effect is small. A large volume effect signifies that the NTCP correlates with the mean dose, while a small volume effect implies that the NTCP correlates with the maximum dose in the OAR (Mayles et al. 2007).

**Figure II.21:** Organ architecture: Serial organs (a) are assumed to be comprised of critical FSUs, analogous to links in a chain, and when one FSU is damaged the entire organ is compromised and complications ensue. Organs with this architecture reveal a weak volume effect. As for organs with parallel architecture (b), it is assumed that they are arranged in such a fashion that complications only occur once a sufficient proportion of the FSUs, known as the functional reserve, have been incapacitated. Serial-parallel organs (c) are an amalgamation of the previous two. Adapted from (Kallman et al. 1992).

NTCP can also be determined through equation II.24, also known as the relative seriality NTCP model.

$$NTCP = \left[ 1 - \prod_{j=1}^{k} \left( 1 - NTCP(D_j)^{s} \right)^{v_j} \right]^{\frac{1}{s}}$$

(II.23)
This model is built on binomial statistics and therefore has a mechanical radiobiological pedigree (Kallman et al. 1992), it handles serial and parallel architecture using FSU. Equation II.24 describes the response of the whole organ to an arbitrary dose distribution \( (D_j, v_j) \) as a function of the response of the whole organ to a homogeneous dose distribution. The number of FSU corresponds with the \( k \) bins in the DVH, and \( s \) is the relative seriality factor. When \( s \) is large the FSUs can be considered to be in series, when \( s \) is small the FSUs can be assumed to be arranged in parallel. \( NTCP(D_j) \) can be expressed as:

\[
NTCP(D_j) = 2^{\exp(\gamma(1 - \frac{D_j}{D_{50}}))}
\]

(II.24)

Which is based on Poisson statistics to describe cell survival. The \( \gamma \) parameter is the maximum relative slope of the dose response curve and \( D_{50} \) is the whole organ uniform dose that would produce a 50% complication probability.

II.7 Preference for the LKB NTCP model

A seminal paper investigating the tolerance of normal tissue to therapeutic irradiation (Emami 1991) is the most frequently reference paper ever published in the International Journal of Radiation Oncology Biology Physics, with 1,062 citations according to the ISI Web of Science (accessed February 3, 2009). The study produced tolerance doses for irradiation of one third, two thirds, or the whole of various organs. The authors took a bold approach, due to the lack of good quality clinical data, to ascertain these doses through a simple consensus of clinical experience. A complementary paper (Burman et al. 1991) fitted the Lyman NTCP model (Lyman 1985) to the consensus dose volume data thereby facilitating the use of dose volume constraints for an arbitrary fraction of a whole organ uniformly irradiated. Additionally, (Kutcher et al. 1991) proposed an algorithm for DVH reduction, effectively enabling the extrapolation of dose volume constraints to any dose distribution. This LKB model remains the most widely
used NTCP model. Although the LKB NTCP model cannot claim a profound mechanistic validity, its mathematical construct is suitably supple to allow representation of various dose volume dependencies. Within the structural resolution of current datasets, the LKB NTCP model can typically not be rejected as a good fit of the data (Bentzen et al. 2010). It is on these grounds that the selection of the LKB NTCP model, for all NTCP calculations in this thesis, is made.

II.8 Fitting the NTCP Model

The NTCP model (Lyman 1985) was fitted to the Emami/Burman data set using the values in Table II.6 obtained from the literature (Burman et al. 1991). The clinical end points are those defined by the radiation therapy oncology group (RTOG) and the European organisation for research and treatment of cancer (EORTC).

<table>
<thead>
<tr>
<th>Organ</th>
<th>Model parameters</th>
<th>Clinical end point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$  $m$  $TD_{50}$</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>0.12 0.15 80 Gy</td>
<td>Severe proctitis/necrosis/stenosis/fistula</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.5 0.11 80 Gy</td>
<td>Symptomatic bladder contracture</td>
</tr>
<tr>
<td>Femoral head</td>
<td>0.25 0.12 65 Gy</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

The NTCP model matches the clinical data for the rectum, bladder and femoral heads exceptionally well, however it must be noted that this data set is for whole organ irradiation and is now 18 years old, derived from pre-CRT/IMRT clinical data. Justification for the use of the original LKB NTCP model fit can be made on the grounds that if the mathematics of equation II.20 for the EUD are correct, then the model should hold true, and therefore accurately predict today’s complex treatments. A modern review of the clinical response of OARs was required and has recently been published by the quantitative analysis of normal tissue effects in the clinic (QUANTEC) steering committee. The Steering Committee defined three aims for QUANTEC.
1. To provide a critical overview of the current state of knowledge on quantitative dose-response and dose-volume relationships for clinically relevant normal-tissue endpoints.

2. To produce practical guidance allowing the clinician to reasonably (though not necessarily precisely) categorise toxicity risk based on dose-volume parameters or model results therapy.

3. To identify future research avenues that would help improve risk estimation or mitigation of early and late side effects of radiation therapy.

The QUANTEC review provides focused summaries of the dose/volume/outcome information for many organs, including the rectum and bladder but excluding the femoral heads. In the case of the rectum, obtainable dose/volume/outcome data for rectal injury was reviewed. The volume of rectum receiving $\geq 60$ Gy is consistently connected with the risk of grade $\geq 2$ rectal toxicity (RTOG/EORTC: Moderate diarrhoea and colic, bowel movement $\geq 5$ times daily, excessive rectal mucus or intermittent bleeding). Parameters for the LKB NTCP model from four clinical studies are remarkably consistent (Cheung et al. 2004; Rancati et al.)
Biological models

2004; Sohn et al. 2007; Tucker et al. 2007), indicating that high doses are chief in determining the risk of toxicity. The best general estimates (95% confidence interval) of the LKB NTCP model parameters are $\frac{1}{a} = 0.09$ (0.04-0.14); $m = 0.13$ (0.10-0.17); and $TD50 = 76.9$ (73.7-80.1) Gy (Michalski et al. 2010). Most of the models of late radiation toxicity come from 3D CRT dose escalation studies of early stage prostate cancer. It is possible that IMRT or proton beam dose distributions require modification of these models because of the inherent differences in low and intermediate dose distributions.

\[ D = \frac{aE + b}{(1 + \frac{E}{c})^m} \]

\[ TD50 = D \frac{1}{\alpha/\beta} \]

Figure II.23: DVH thresholds associated with rectal toxicity: Thicker lines indicate higher rates of occurrence of overall grade $\geq 2$ toxicity (percentages are indicated on the graph along with the physical prescription dose). Threshold doses are expressed as LQ equivalent doses delivered in 2 Gy fractions, calculated using $\alpha/\beta = 3$ Gy. The associated LQ equivalent prescription doses are coded by spectrum from lowest (blue), to highest (red). Volumes shown in the graph are based on the full length of the anatomic rectum. Curves for Huang and Wachter were adjusted downward by 15% and by 50% for Hartford, to account for the different definitions used for rectal volume. Dose volume data from multiple centres converge at the high dose range, implying that these values are more consistently associated with toxicity. Extracted from (Michalski et al. 2010).

In the case of the bladder, a comprehensive overview of the normal tissue radiation
tolerance was conducted. The most instructive investigations considered whole
organ irradiation as the data on partial organ and nonuniform irradiation is
suspect due to organ motion not being accounted for, and many studies lack long
enough follow-up data. Future studies are required to further refine modelling
parameters for the bladder.

II.9 Discussion of NTCP model parameters

Traditionally, RT fields and doses were determined empirically, founded mainly
on clinical experience. Physicians relied on intuition to select field sizes and doses.
However it is widely accepted by clinicians that these empiric guidelines are im-
precise and do not completely describe the underlying anatomy, physiology, and
dosimetry. When 3D dosimetric data became extensively available, guidelines
were necessary to aid physicians predict the relative safety of competing treat-
ment plans, although only limited data was available. So in 1991, investigators
gathered and pooled their collective clinical experience, judgement, and informa-
tion regarding partial organ tolerance doses, and produced values for dose volume
tolerance of many organs (Emami 1991). While this work is often criticised, the
study plainly states the uncertainties and limitations in its recommendations, and
it is widely admired for addressing a pressing clinical concern. Over the past two
decades, numerous investigations have reported links between dosimetric param-
eters and normal tissue toxicity outcomes. The QUANTEC initiative summarises
the available data to update and refine the estimates previously provided. The
information provided by QUANTEC is not ideal, and care must be taken to apply
it correctly in the clinic. The data reviewed is principally extracted from publica-
tions. Because different investigators often present information differently (e.g.,
actuarial vs. crude complication rates), pooling data from multiple studies may
be inaccurate. Despite these caveats, model based risk estimates are an actual-
ity. Physicians regularly use models, in their broadest sense, to make treatment
decisions. Use of metrics such as the mean dose and maximum dose to estimate
risk for parallel and serial organs are models, albeit simple ones. NTCP models
attempt to reduce complicated anatomic, physiologic and dosimetric information into a single numeric measure of risk.

II.10 Conclusions for the NTCP model

Two distinctive NTCP models have been presented, first the LKB NTCP model, which is empirical in nature, and second the relative seriality NTCP model, which has a mechanistic construct. The parameters of the LKB NTCP model, $TD_{50}$, $m$, and $n$ have been tabulated previously (Burman et al. 1991) for different organs and specified clinical endpoints, defined by RTOG/EORTC, based on the clinical tolerance data previously published (Emami 1991). To incorporate into the LKB model the more practical scenario of a nonuniform irradiation of a critical organ, a reduction scheme (Kutcher et al. 1991) is used to reduce the DVH to an effective fractional volume uniformly irradiated. The relative seriality NTCP model describes the probability of damage to normal tissue based on binomial statistics. The model accounts for serial and parallel architecture of the FSU which describes the response of the whole organ to an arbitrary dose distribution as a function of the response of the whole organ to a homogeneous dose distribution. The number of FSU has been made to coincide with the $k$ bins in the DVH, and $s$ is the relative seriality factor. The $\gamma$ parameter is the maximum relative slope of the dose response curve and $D_{50}$ is the whole organ uniform dose that would produce a 50% complication probability. The LKB NTCP model currently holds the dominant position within clinical NTCP modelling and is the most extensively used NTCP model. The most frequently reference paper ever published in the International Journal of Radiation Oncology Biology Physics, with 1,539 citations according to the ISI Web of Science (accessed February 20, 2012) employed the LKB NTCP model. Despite the lack of a proper radiobiological mechanistic pedigree, the mathematical makeup of the LKB NTCP model is sufficiently flexible to enable reasonably accurate prediction of various dose volume relationships. We therefore conclude that within the overall precision of present datasets, the LKB NTCP model can be accepted as a good fit of the data and is the most
appropriate NTCP model for the analysis and evaluation of external beam RT plans with regard to normal tissue complication under typical clinical conditions for the treatment of intermediate risk prostate cancer.

II.11 The uncomplicated tumour control probability

To fully incorporate all of the factors which affect the accurate prediction of clinical outcomes a model describing both TCP and NTCP is required. The TCP model is combined with the NTCP model through equation II.25, thus yielding a single numerical indicator of treatment efficacy (Sanchez-Nieto and Nahum 2000). The uncomplicated tumour control probability (UTCP).

\[
UTCP = TCP \prod_{f=1}^{OAR} (1 - NTCP_f)
\]  

(II.25)
The physics of photon and electron interactions in matter is well understood, however it is impossible to describe particle transport in a medium by means of an analytical expression (Rogers 2002). This is because electrons can create both photons through bremsstrahlung, and secondary or knock on electrons. Conversely, photons can create both electrons and positrons through pair production. In addition, during interactions both electrons and photons are highly scattered. MC simulations provide estimated solutions to analytically intractable mathematical problems via computational methods (Fishman 1996). Consequently MC is a technique utilised to simulate the interactions of photons and electrons in matter.

The MC method, used in the simulation of radiation transport, employs computer generated random numbers and the knowledge of the probability distributions governing the individual interactions of electrons and photons in materials to simulate the trajectories or histories of individual particles (Rogers 2002). As a large number of histories are modelled the result approaches the average photon and electron distribution, calculated to within a statistical uncertainty. The level of which decreases inversely with the square root of the computation time (Keall et al. 2000). The ability to simulate RT treatments using this method clearly
Figure III.1: Particle interactions: A high energy photon is incident on a slab of lead from the right. An interaction event produces an electron-positron pair. The positron is scattered and loses its energy, an annihilation event occurs. The electron is also scattered and loses its energy, producing a bremsstrahlung photon. One of the 511 keV photons undergoes Compton scatter, creating another knock on electron. The complexity of all the possible interactions is clear. Reproduced from (Rogers 2002).

facilitates the calculation of accurate dose distributions (Ma and Jiang 1999). When compared to analytical techniques, MC simulation has been proven to be a superior method for modelling dose deposition in regions of varying material density, as encountered in clinical treatments. In the instance of the boundary interface between water and the lung, the difference between dose deposition calculated using an analytical technique with that of MC simulation can be as much as 14% (Sargison et al. 2004). There are several fundamental differences between MC calculated dose distributions and those calculated using traditional analytical algorithms (Verhaegen and Seuntjens 2003). One important difference is the inherent statistical uncertainty associated with MC calculated values. This uncertainty arises from the random sampling used in the MC method and is therefore not present in dose distributions calculated using analytical techniques. The heart of the MC method is a simple computational structure where a process is modelled by producing a large number of possible outcomes. For N events, the mean and variance of a simulation are calculated as.
Monte Carlo modelling in RT

\[ \mu = \frac{1}{N} \sum_{i=1}^{N} x_i \]  \hspace{1cm} (III.1)

and

\[ \sigma^2 = \frac{1}{N-1} \sum_{i=1}^{N} (x_i - \mu)^2 \]  \hspace{1cm} (III.2)

Where \( \mu \) is the mean, \( \sigma^2 \) is the variance and \( x_i \) is considered an independent event. One event is considered independent of another if the occurrence of one gives no information about whether or not the other will occur. The standard error of the mean, \( \delta \), is calculated by:

\[ \delta = \frac{\sigma}{\sqrt{N}} \]  \hspace{1cm} (III.3)

From equation III.3 it is clear that the accuracy of a MC simulation is proportional to \( 1/\sqrt{N} \).

III.1 BEAMnrc and DOSXYZnrc

The OMEGA project was a collaborative project set up between the National Research Council of Canada and the University of Wisconsin-Madison. The aim was to design a full three dimensional electron beam simulation based on MC techniques that could be used to calculate the dose to a RT patient. Developed as part of the OMEGA project, BEAMnrc and DOSXYZnrc are user codes for the original EGSnrc system (Rogers et al. 1995). BEAMnrc and DOSXYZnrc are formalisms for modelling radiation transport from a medical linac and dose deposition in a phantom, respectively. The convention used in building a linac model is to define the z-axis of the simulation as the beam central axis, this axis is then used as the origin for all other spatial requirements. A BEAMnrc model is built by configuring a series of component modules to dimensions provided by the
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manufacturer. The Siemens model was based on information received from the vendor under a non-disclosure agreement. This provided data on the materials and dimensions of the primary beam components of the accelerator head. The accelerator head was modelled using the following component modules (CMs) to model the corresponding linac components.

- FLATFILT CM used to create the accelerator tungsten target.
- FLATFILT CM used to create the primary collimator and flattening filter of the accelerator.
- CHAMBER CM used to create the photon dose chamber.
- MIRROR CM used to create the photon mirror.
- JAWS CM used to add a pair of Y jaws to the model.
- MLC CM used to model the MLC of the Siemens accelerator.
- SLABS CM used to add an air slab to the end of the accelerator to bring the model to the desired distance from the source.

The primary output of a BEAMnrc simulation is a phase-space file. This file contains information on all the particles crossing the xy-plane located at a fixed point along the z-axis. The xy-plane is referred to as a scoring plane; any number of scoring planes can be defined and located anywhere in the accelerator head. A phase-space file contains information on each particle, such as: charge, energy, position, direction, LATCH. DOSXYZnrc, used in combination with the EGSnrc simulation code, facilitates the calculation of dose distributions within a rectilinear phantom. The code uses sources such as mono-energetic diverging or parallel beams, as well as phase-space data generated by BEAMnrc simulations. Photon-electron transport is simulated in a Cartesian volume and energy deposition scored in designated voxels. Each voxel is assigned a physical density that represents the true material confined to that voxel. The dimensions of each voxel
can be varied but are usually of the order of 0.1–1.0 cm$^3$. For any given simulation a phantom is configured as an array of voxels. CT based phantoms can be modelled in DOSXYZnrc by processing CT data using the program ctcreate. The dose distributions in phantoms derived from patient CT data sets, can thus be calculated.

In DOSXYZnrc statistics are handled by grouping scored quantities on a history by history basis. Uncertainties ($s_X$) are determined for each scored quantity $x_i$ as statistically independent events, ($s_X$) is given by (Walters et al. 2002).

$$ (s_X) = \sqrt{\frac{1}{N-1} \left( \frac{\sum_{i=1}^{N} x_i^2}{N} - \left( \frac{\sum_{i=1}^{N} x_i}{N} \right)^2 \right)} \quad \text{(III.4)} $$

Here N is the total number of independent events and is always equal to the total number of primary histories. Using this method, a statistical dose uncertainty for each voxel can be calculated as a function of initial history number. For phase-space sources generated using BEAMnrc there is potentially more than one particle in the file that may be traced back to the same initial primary history. Therefore, to account for a common initial history, the history by history technique groups all particles according to the primary history that generated each and calculates the uncertainty accordingly.

### III.2 The Siemens Oncor models tuned

MC simulations of particle transport is the most accurate method of calculating dose (Verhaegen and Seuntjens 2003). However, MC simulations are only as accurate as the level to which they have been tuned. Therefore, an accelerator model must initially be tuned to an acceptable degree of accuracy before being used to calculate treatment plans or for examining accelerator dose distributions. For the purposes of this work an acceptable level of accuracy is deemed to be an overall average discrepancy of $\leq 3\%$ (Ma and Jiang 1999) with the requirement
that this discrepancy fall to $\leq 1\%$ after $D_{\text{max}}$ and within the flat field of the beam. This is in keeping with the achievable accuracy of most clinically relevant measurements (Ahnesjo and Aspradakis 1999). The tuning process for the 6 MV model was carried out according to a methodology developed here in the MPRC (Conneely 2011). This methodology has 4 phases. Phase 1 begins by selecting a broad range of primary electron beam energy values (5.5 - 6.5 MeV) and radius values (0.05 cm - 0.20 cm) for large field profiles ($20 \times 20$ cm$^2$). Phase 2 fine tunes the energy of the electron beam. Phase 3 examines output factors for a range of field sizes ($4 \times 4$ cm$^2$ - $40 \times 40$ cm$^2$). The process culminates with phase 4, measurements and MC simulations of percentage depth dose (PDD) and transverse dose profile (TDP) curves for a range of field sizes for the tuned parameters are compared.

![Percentage depth dose curve](image1)

![Transverse dose profile curve](image2)

**Figure III.2:** Profile analysis: PDD and TDP curves for the tuned 6 MV Siemens photon model compared with QA measurements for square fields of $10 \times 10$ cm$^2$ size. Residual analysis shows an upper limit of $\pm 0.5\%$ disagreement between the MC simulation and the QA measurement along the PDD profile after $D_{\text{max}}$, with $\pm 0.6\%$ disagreement between the MC simulation and the QA measurement in the flat field of the beam. Analysis also shows accuracy of up to $\pm 1$ mm in the penumbra and build-up region.
The tuning process for the 6 MV model was carried out previously, (Conneely 2011). The tuning process for the 15 MV model was also conducted according to a similar methodology.

III.2.1 The 15 MV Siemens Oncor model tuned

This section of the work aimed to verify the efficacy and simplicity of a previously established tuning method (Conneely 2011) by using it to tune a Siemens Oncor accelerator for 15 MV photon beams. The electron beam entering the linac model was assumed to be mono-energetic with a circular cross section and with a Gaussian spread (Sheikh-Bagheri and Rogers 2002) characterised by a full width half maximum (FWHM) distance (ISOURCE19). Measurements taken from GUH RT department were used in the tuning process of the Siemens Oncor 15 MV model. The most readily available dose profile data from the QA process was the $10 \times 10 \text{ cm}^2$ field, so this was the field used for the initial tuning process. The final parameters are verified for PDDs and TDPs for different square fields using available measurement data. Images of the equipment used and of the setup are shown in figures III.3 and III.4, respectively.

![Image of equipment](image-url)

**Figure III.3:** The LA48 linear array detector: The measurements from the RT department in GUH were performed using a linear array detector (LA48) with an air-scanner adapter (*PTW, Germany*). Extracted from (Conneely 2011).

Figure III.5 displays the tuning process as applied to the 15 MV Siemens Oncor accelerator model in this work.
Figure III.4: Images taken of the measurement setup during the Siemens QA process: The LA48 with an air-scanner adapter is scanned through a $40 \times 40 \times 40$ cm$^3$ water tank with measurements taken down to a depth of 34 cm for the PDD. For the dose profile in the X and Y directions measurements are taken from -11 cm to +11 cm from the central axis position for the $10 \times 10$ cm$^2$ field. Measurements are taken at minimum and maximum increments of 0.1 and 1.0 cm respectively. Extracted from (Conneely 2011).

III.2.2 Input parameters

The EGSnrc physics parameters used in the input files for both the BEAMnrc and DOSXYZnrc parts of the simulations for tuning the 15 MV Siemens Oncor accelerator model are listed in Table III.1. The same parameters were used for all phases of the tuning process. These were the default transport options. There was no electron splitting and range rejection was not used. These same inputs were used for each phase of the process. The MC simulations were conducted in two stages. The input parameters used for the MC simulations are given Table III.3. Initially the BEAMnrc code was used to simulate the transport of the particles through the linear accelerator model to the scoring plane and were stored in a phase-space file. Subsequently, this phase-space file was used as the input for the DOSXYZnrc code which simulates the transport and energy deposition of
the particles in the water phantom. The pegs4 data file was oncor-materials-521icru.pegs4dat. The voxel dimensions of the water phantom used in the MC simulations are listed in Table III.2.

III.2.3 Phase 1 - Energy & FWHM of the incident electron beam

For the initial tuning process, root mean squared difference (RMSD) values were calculated for MC simulation and measurement of the PDD profile of a $10 \times 10$ cm$^2$ field of the Siemens Oncor 15 MV linac. Measurements, in the water
phantom shown in figure III.4, and MC simulation were between 0 cm and 20 cm depth along the Z axis at the central axis (CAX) position. MC simulations were run for 13.0, 14.0 and 15.0 MeV with FWHMs of 0.05, 0.10, 0.15, 0.20 cm.
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Figure III.6 shows the MC simulation results of phase 1, PDD profiles of a $10 \times 10$ cm$^2$ field overlaid upon clinical measurements. The RMSD values calculated for each MC simulation of phase 1 are displayed in Table III.4.

\textbf{FIGURE III.6:} Tuning curves for Phase 1: PDD curves for the 15.0 MV Siemens photon models compared with QA measurements for square fields of $10 \times 10$ cm$^2$ size. RMSD values were calculated based on these curves, the disagreement between the MC simulation and the QA measurement along the PDD profiles indicates that the tuned energy source lies somewhere between 13.0 MeV and 14.0 MeV.

\textbf{TABLE III.4:} RMSD values for phase 1 of the tuning process

<table>
<thead>
<tr>
<th>Source energy (MeV)</th>
<th>FWHM (cm)</th>
<th>RMSD$_z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.0</td>
<td>0.05</td>
<td>0.3019</td>
</tr>
<tr>
<td>13.0</td>
<td>0.10</td>
<td>0.2097</td>
</tr>
<tr>
<td>13.0</td>
<td>0.15</td>
<td>0.3915</td>
</tr>
<tr>
<td>13.0</td>
<td>0.20</td>
<td>0.3998</td>
</tr>
<tr>
<td>14.0</td>
<td>0.05</td>
<td>0.4024</td>
</tr>
<tr>
<td>14.0</td>
<td>0.10</td>
<td>0.2931</td>
</tr>
<tr>
<td>14.0</td>
<td>0.15</td>
<td>0.3941</td>
</tr>
<tr>
<td>14.0</td>
<td>0.20</td>
<td>0.4736</td>
</tr>
<tr>
<td>15.0</td>
<td>0.05</td>
<td>0.6792</td>
</tr>
<tr>
<td>15.0</td>
<td>0.10</td>
<td>0.6417</td>
</tr>
<tr>
<td>15.0</td>
<td>0.15</td>
<td>0.6605</td>
</tr>
<tr>
<td>15.0</td>
<td>0.20</td>
<td>0.5191</td>
</tr>
</tbody>
</table>

These MC simulations had an average uncertainty of approximately ±1.0%.
III.2.4 Phase 2 - Fine tuning the Energy & FWHM

Subsequent to phase 1 it was clear that the best value for the initial electron energy lay somewhere in the region between 13.0 MeV and 14.0 MeV for the accelerator model, as the measured PDD curve fell between the curves obtained at these two energies. Consequently, it was decided to continue the tuning process by now including the TDP curves obtained from QA measurement. The tuning process was resumed using initial electron energies of 13.0, 13.5, 14.0 MeV, while once again using the same values for the FWHM of the radius of the incident electron beam of 0.05, 0.10, 0.15, 0.20 cm. In phase 2 RMSD values were calculated for each plane of measurement for the 15 MV Siemens Oncor photon model. PDD profile measurements and MC simulations along the Z axis at the CAX position were between 0 cm and 20 cm depth. TDP measurements and MC simulations along the X and Y axes were between -7.5 cm and +7.5 cm from the CAX position at 10 cm depth in the water phantom, see Figure III.4. Table III.5 shows that the values for the energy of the incident electron beam and FWHM of the incident electron beam are located at 13.5 MeV and 0.15 cm respectively.

<table>
<thead>
<tr>
<th>Energy (MeV)</th>
<th>FWHM (cm)</th>
<th>RMSD$_z$</th>
<th>RMSD$_x$</th>
<th>RMSD$_y$</th>
<th>RMSD$_{xyz}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.0</td>
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<td>0.3019</td>
<td>0.5838</td>
<td>1.3843</td>
<td>0.7567</td>
</tr>
<tr>
<td>13.0</td>
<td>0.10</td>
<td>0.2097</td>
<td>0.4898</td>
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<td>0.05</td>
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<td>0.10</td>
<td>0.4911</td>
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<td>0.7305</td>
</tr>
<tr>
<td>13.5</td>
<td>0.15</td>
<td>0.2287</td>
<td>0.4506</td>
<td>1.1097</td>
<td>0.5963</td>
</tr>
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<td>0.20</td>
<td>0.4678</td>
<td>0.5237</td>
<td>1.1039</td>
<td>0.6985</td>
</tr>
<tr>
<td>14.0</td>
<td>0.05</td>
<td>0.4024</td>
<td>0.5641</td>
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<td>0.7569</td>
</tr>
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<td>14.0</td>
<td>0.10</td>
<td>0.2931</td>
<td>0.5260</td>
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<td>0.6670</td>
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<td>14.0</td>
<td>0.15</td>
<td>0.3941</td>
<td>0.4892</td>
<td>1.1063</td>
<td>0.6632</td>
</tr>
<tr>
<td>14.0</td>
<td>0.20</td>
<td>0.4736</td>
<td>0.5918</td>
<td>1.1086</td>
<td>0.7247</td>
</tr>
</tbody>
</table>
III.2.5 Phase 3 - Verification of the tuning results

The final phase of the tuning process compared the accuracy of the MC calculated PDD and TDP curves at 10.0 cm depth for field sizes of $5 \times 5$ cm$^2$, $10 \times 10$ cm$^2$, and $20 \times 20$ cm$^2$ for the chosen parameters of 13.5 MeV energy and 0.15 cm FWHM of the incident electron beam, against measured data. These dose profiles along with residual and distance to agreement (DTA) analysis of the data, calculated using linear interpolation (Downes 2010), is displayed in Figure III.8.

III.3 Discussion of the tuned 15 MV Siemens Oncor model

For the 15 MV Siemens Oncor linac, the MC dose profile simulations along with the RMSD analysis of the measured data indicated that an energy of 13.5 MeV
for the incident electron beam together with a radial distribution of 0.15 cm for
the beam radius produced the best fit with the least variance to the measured
data. These parameters produce a MC value, on average after $D_{max}$ and within
the flat field of the beam, within $\pm 1.0\%$ of the measured data for the PDD and
TDP curves simulated for the different field sizes ($20 \times 20$ cm$^2$, $10 \times 10$ cm$^2$,
$5 \times 5$ cm$^2$). For this Siemens Oncor 15 MV model, the PDD profiles for all
the field sizes agree with measurement within $\pm 1.8\%$ after $D_{max}$. The TDPs of
the Siemens model for all field sizes agree within $\pm 1.6\%$ inside of the penumbra.
Overall, the maximum percentage difference was within $\pm 11.6\%$ with a maximum
DTA of $\pm 4$ mm for all field sizes. No attempt was made to match the asymmetry
in the beams of GUH (Sawkey and Faddegon 2009b), this lead to a $\pm 11.6\%/4$mm
discrepancy between simulation and measurement. The $20 \times 20$ cm$^2$ field size
is the limiting field size with the worst agreement between simulation and mea-
surement. It has previously been shown that in order to produce good agreement
in the Siemens Oncor accelerator model for all field sizes, different tuned values
are required for the FWHM of the radius of the primary electron beam for small
fields (below 10 cm) and large fields (10 cm and greater) (Conneely 2011). Work
by (Jaffray et al. 1993) has shown the reason for this is that the size of the inci-
dent electron beam varies with changes in the field size, due to partial blocking of
the extra-focal portion of the source by the secondary collimators. This effect is
also in keeping with what has been previously implemented in the TPS in GUH,
where this Siemens linac is in use clinically. The tuned values for the beam radii
used in the TPS for the Siemens linac are 0.1505 cm for small fields and 0.1725
cm for large fields (Conneely 2011). As the $20 \times 20$ cm$^2$ field size is not clin-
ically applicable (Pena et al. 2007; Conneely 2011) to prostate treatment, field
sizes typically between 4-8 cm$^2$, it can be omitted from further analysis. Neglect-
ing this field size and the penumbra region results in a new overall agreement
of $\pm 3.8\%/2$ mm. This level of accuracy is suitable for deeply situated tumours
within patients, such as prostate cancer. These limitations in accuracy are in line
with those reported previously (Downes 2010; Conneely 2011). For the purposes
of this investigation an accuracy of approximately 3% with the requirement that
this fall to $\leq 1\%$ after $D_{\text{max}}$ and within the flat field of the beam was deemed adequate. This is consistent with the realisable accuracy of most clinically relevant measurements (Ahnesjo and Aspradakis 1999).

An efficient tuning method has been implemented using the EGSnrc code. The aim was to ascertain a model that agreed to measured data, so that it could be used as a verification tool for non-standard clinical treatment plans. This work shows that the goal of establishing a convenient and minimally time intensive method for linac model tuning, suitable for clinical implementation has been achieved as per the methodology developed here in the MPRC (Conneely 2011). A superior tuned model is obtainable, MC simulations are only as accurate as the level to which they have been tuned. In order to obtain an improved model output factors should be simulated and compared with measured data. The energy and FWHM of the incident electron beam could be investigated further, between 13.0 MeV and 14.0 MeV at step sizes of 0.1 MeV and 0.01 cm. The range of field sizes could be increased from very small to very large, $1 \times 1 \text{ cm}^2$ to $40 \times 40 \text{ cm}^2$. The emphasis here should be on the smaller field sizes as they are clinically more relevant (Pena et al. 2007; Conneely 2011).

The quantity of published work on the process of tuning a Siemens accelerator model (and in particular the Oncor accelerator) is relatively limited when compared to Varian accelerators. A previous study similar in nature to this work investigated the tuning of the Siemens Oncor accelerator with fields of $5 \times 5 \text{ cm}^2$ for depth dose curves and fields of $40 \times 40 \text{ cm}^2$ for dose profiles by (Sawkey and Faddegon 2009a). Further work by (Sawkey and Faddegon 2009b) involved the dismantling of a research accelerator and removal of the flattening filter in order to achieve a very accurate model.
Figure III.8: Profile analysis: PDD and TDP curves for the tuned 15 MV Siemens Oncor photon model compared with QA measurements for square fields of $5 \times 5$ cm$^2$, $10 \times 10$ cm$^2$ and $20 \times 20$ cm$^2$ size. Residual analysis shows an upper limit of $\pm 1.8\%$ disagreement between the MC simulations and the QA measurements along the PDD profile after $D_{\text{max}}$, with an average deviation of $\pm 0.9\%$ across the range simulated. Furthermore, the analysis shows an upper limit of $\pm 1.6\%$ disagreement between the MC simulations and the QA measurements in the flat field of the beam with an average deviation of $\pm 0.3\%$ across the range simulated. The dashed coloured lines represent the mean deviations of the simulations across the full range of measurements, including the build-up and penumbra regions. Overall, the maximum percentage difference was within $11.6\%$ with a maximum DTA of 4 mm. No attempt was made to match the asymmetry in the beams of GUH. The $20 \times 20$ cm$^2$ field size is the limiting field size with the worst agreement between simulation and measurement. As this field size is not clinically applicable (Pena et al. 2007; Conneely 2011), it can be omitted from further analysis. Neglecting this field size and the penumbra region, new overall agreement of $3.8\%/2$ mm results.
III.4 DICOM files

The DICOM standard was developed in collaboration with vendors to allow different systems to communicate with each other in a well defined way. DICOM is a file transfer standard and a file format, vendors that support any part of the standard have to issue a conformance statement declaring which parts of the standard are supported. The DICOM standard is ubiquitous within medicine. In relation to RT, there are a number of specific types of DICOM files that are commonly referred to as DICOM-RT, the RT extension of DICOM. These files hold the relevant planning information for treatment.

- **RT-PLAN**: files contain treatment plan specific information.
- **RT-DOSE**: files contain dose information for a treatment plan.
- **RT-STRUCT**: files contain RT-structure set information.
- **RT-IMAGE**: files contain the re-constructed radiograph information.
- **DICOM-CT**: files contain an accurate representation of the patient anatomy.

Patient planning is performed using a TPS. With the DICOM standard, it is possible to export a plan from a TPS in a standard way to recreate that plan and verify the treatment delivered. In order to recreate a treatment plan and a representation of the patient it is essential to possess the relevant plan information. In order to carry out verification of a treatment, it is also necessary to have the dose distribution and the RT-structure sets. The RT-structures are necessary so that dose to the volumes of interest (VOIs), such as GTV and OARs, can be compared. MC simulation is perfect for treatment verification. Currently it is the most accurate algorithm accessible, there are however some issues that ought to be addressed before a treatment plan may be simulated correctly. The convention for the coordinate system in DICOM is different to the convention of coordinate
system in EGSnrc, and it is imperative to convert to the coordinate system of the MC code. It is also crucial that the CT information is correctly converted so that it can be used for MC simulation. Finally, MC simulations report dose-to-medium and, typically, TPSs report dose-to-water. Therefore the dose needs to be converted from dose-to-medium to dose-to-water for direct comparison.

III.5 The MMCTP code

Figure III.9 shows the user interface of the MMCTP system.

![Figure III.9: MMCTP user interface: The external beam window showing the patient plan on the left, three canvas views for axial, sagittal and coronal display and the tab menu. The dose distribution shown is a MC simulation.](image-url)
Monte Carlo modelling in RT

The MMCTP code was developed in the Medical Physics Unit at McGill University. MMCTP was designed to be a versatile radiotherapy research environment which would enable MC calculated dose distributions to be compared with those from commercial TPSs. Thus enabling large scale retrospective and prospective patient treatment studies (Alexander et al. 2007). The shortcomings of TPSs are well known as they use a number of approximations in order to increase the speed of the calculations. These inaccuracies are borne out in scenarios with severe tissue heterogeneities for example the air cavity of the lungs (Sargison et al. 2004) or the femoral heads in prostate cancer (Fraser et al. 2008) treatment. MMCTP provides the ability to examine and assess the accuracy of TPSs compared to MC calculations using an unbiased independent common platform.

Features of the MMCTP system:

- File imports: MMCTP has the ability to import treatment plans of DICOM-RT format. Including beam geometry properties, CT images and RT-structures. Treatment plans in the DICOM-RT format from GUH have been successfully imported.

- Plan visualisation: MMCTP has the ability to superimpose RT-structure and dose distributions on to CT images, thereby visualising treatment plan information in either a 2D or 3D context.

- Dose analysis tools: MMCTP has the ability to analyse the dose distributions from individual or combined beams. DVHs can also be calculated and analysed for plan evaluation.

- Editing of treatment plans: MMCTP also allows the user to edit treatment plans, by adding or deleting beams and editing of beam properties such as weighting, rotation, field size, and iso-center.

- Monte Carlo calculations: MMCTP automatically prepares the input files required for MC simulation based on the external beam geometry and image structures imported from the DICOM-RT file. The MC calculations are performed on a remote cluster using the BEAMnrc code.
The computing resources used for dose distribution calculation using MMCTP were performed on Chevron, a Studio XPS 8100 (Dell\textsuperscript{TM}, RoundRock, Texas) eight core i7 (Intel\textsuperscript{TM}, MountainView, California) central processing unit (CPU).

III.6 Absolute dosimetry in MC simulations

To accurately model RT treatment plans using the MC method an absolute dosimetric reference frame must be established. The reference frame is a requirement if MC dose distributions are to be clinically useful. Therefore, the clinical interpretation of a MC dose distribution that is dosimetrically correct, must be related back to a standards laboratory calibration of the modelled linac. A detailed method for determining an absolute dosimetric reference frame to be used for MC simulations has been developed (Popescu et al. 2005). The implementation of this methodology for MC simulation can be done as follows: a phase-space is scored under the fixed component modules of the linac. This phase-space is subsequently used as a source for simulations through the variable component modules, such as the y-jaws and the MLC. The MC simulation of the fixed components of the linac is referred to as the \textit{BEAM\textsubscript{A}} simulation, yielding a phase-space \textit{A} scored above the jaws and a dose \(D_{\text{ch}}^{\text{forward}}\) accumulated in the monitor chamber due to the beam entering the chamber from above. This phase-space is then used as a source for a \textit{BEAM\textsubscript{B}} simulation, yielding a phase-space \textit{B} scored below the jaws and a dose \(D_{\text{ch}}^{\text{back}}\) accumulated in the monitor chamber due to the particles backscattered from the y-jaws and MLC. The mirror and monitor chamber are included in the \textit{BEAM\textsubscript{B}} simulation. This enables the backscattered dose for every simulated field to be obtained, separately from the forward dose, while insignificantly increasing the CPU time per history. With the phase-space designations and monitor unit (MU) chamber dose scored for both forward and backward scattered particles, a convention for calculating the dose as a function of MU’s can be established (Popescu et al. 2005). The final form of the dose MU equation is given by.
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Figure III.10: Schematic of the MC setup: The BEAM simulation involves both the fixed and variable component modules of the linac: target, primary collimator, flattening filter, monitor chamber, mirror, y-jaws, MLC, and air slab. The output is a phase-space scored above the DOSXYZ phantom. This phase-space is then used as a source for the DOSXYZ simulation.

\[ D_{xyz,abs} = D_{xyz} \left( \frac{D_{ch}^{forward} + D_{ch}^{back(10\times10)}}{D_{ch}^{forward} + D_{ch}^{back}} \right) \left( \frac{D_{cal}^{xyz,abs}}{D_{cal}^{xyz}} \right) MU \]  

This equation has a very simple structure, since the only inputs specific to the
phantom and the simulated field are $D_{xyz}$ and $D_{ch}^{\text{back}}$. All others are constants which need to be determined only once. These quantities completely determine $D_{xyz,\text{abs}}$ for a given number of MU. Equation III.5 relates relative MC dose to an absolute dosimetric reference frame associated with standard calibration conditions. The method is easily implemented facilitating the potential application of MC as an accurate description of the dose to be delivered for a given treatment plan in clinical RT. In investigating the modelling of the Varian 2100 linac, it was found that it is important to include backscatter from the jaws into the monitor chamber, otherwise an error of up to 2% could be introduced depending on field size (Popescu et al. 2005). It is a known issue that there is a large amount of backscatter from the Varian 2100 linacs (Liu et al. 2000). The backscatter into the monitor chamber for the Siemens Oncor has been investigated (Downes 2010) and it has been found that the contribution of backscatter to the overall dose was negligible ($\leq 0.02\%$). For this reason, a single factor has been used to calibrate all MC simulations for a particular energy. Experimental measurements were taken for the 6 MV and 15 MV beams delivering a $10 \times 10 \, \text{cm}^2$ field at 100 cm source-to-surface distance (SSD) in a water phantom. The same set-up was modelled with BEAMnrc/DOSXYZnrc using the tuned MC model. A calibration factor was calculated using the following equation (Spezi et al. 2002).

$$k_{MC} = \frac{D_{cal}^{xyz}}{D_{cal}^{xyz,\text{abs}}},$$  

where $D_{cal}^{xyz}$ and $D_{cal}^{xyz,\text{abs}}$ represent the average doses between the depths of 5 cm and 15 cm for MC and measurement, respectively.

When treatment of a patient is being planned, the plan is based on achieving the prescribed dose to the PTV and minimising the dose to the surrounding organs at risk. This dose is in Gy and in MC simulations the dose reported is in dose per particle, typically, Gy per particle. Treatment machines measure the delivery of MUs and are calibrated under reference conditions to deliver a set amount of
Monte Carlo modelling in RT

radiation for 1 MU. Conventionally, the set amount is that 1 MU is equivalent to 0.01 Gy at $D_{\text{max}}$ for a $10 \times 10$ cm$^2$ field at 100 cm SSD, giving a calibration factor, $k = 0.01$ Gy/MU. This is measured in a water phantom. Modelling the same conditions with MC, a calibration factor, $k_{MC}$, can be calculated at the same point as the machine is calibrated. Using equation III.7 any prescribed dose may be calculated.

$$D_{xyz,\text{abs}} = D_{xyz} \frac{k}{k_{MC}} \text{MU} \tag{III.7}$$

Where $D_{xyz,\text{abs}}$ is the absolute physical dose deposited, $D_{xyz}$ is the calculated MC dose output from the simulation and MU is the prescribed MUs. The prescribed MUs can be obtained from the TPS.

### III.7 Dose-to-medium to dose-to-water conversion

Absorbed dose-to-medium $D_{med}$ can be converted to absorbed dose-to-water $D_w$ for photon beam irradiation using Bragg-Gray cavity theory (Bragg 1912; Gray 1936; Attix 1986; Brahme et al. 1988). Bragg-Gray cavity theory and its expansion the Spencer-Attix cavity theory (Spencer and Attix 1955) have been successfully applied to ionisation chamber dosimetry (AAPM-TG-21 1983; ICRU 1984; Attix 1986). Bragg-Gray cavity theory is appropriate when the cavity material does not perturb the fluence of charged particles that would have existed if the cavity was equivalent to the contiguous material. With regard to the case of photons, the ranges of the secondary electrons are required to be much larger than the dimensions of the cavity i.e. the cavity does not ’perturb’ the electron fluence, which is then therefore entirely characteristic of the surrounding medium. In practice, for photons with megavoltage energies, the only dosimeter that really meets this prerequisite is the gas filled ionisation chamber (Ma and Nahum 1991). The Bragg-Gray cavity theory requires that delta-ray (secondary
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electron) equilibrium exists or that the energy transferred to delta-rays is deposited 'locally'; it is evaluated by use of the primary electron fluence and the unrestricted collision stopping powers, equations III.8 and III.9. Spencer-Attix theory (Spencer and Attix 1955; ICRU 1984) uninvolved this limitation in an approximate fashion by including delta-rays in the fluence of charged particles entering the cavity, and then using the stopping power restricted to losses less than $\Delta$, where this cut off energy is related to the size of the cavity. For small cavities such as ion chambers $\Delta$ is generally set equal to 10 keV (Nahum 1978; ICRU 1984). It can be noted that, somewhat paradoxically, the greatest deviation between the Bragg-Gray and Spencer-Attix values for the stopping-power ratio occur for the smallest values of $\Delta$ i.e. for the smallest cavities. To circumvent the unnecessary issues introduced by the selection of the Spencer-Attix cut off energy, consider a hypothetical Bragg-Gray water cavity in which delta-ray equilibrium is established. Thus the conversion can proceed as follows. Using Bragg-Gray cavity theory, the absorbed dose-to-water is related to the absorbed dose-to-medium by (Siebers et al. 2000).

$$D_w = D_{med} S_{w,med}$$  \hspace{1cm} (III.8)

Where $S_{w,med}$ is the unrestricted water-to-medium mass collision stopping power ratio averaged over the energy spectra of primary electrons, $(\Phi_E)_m$. The primary electrons do not include knock on electrons or delta-rays, as their contributions to energy deposition are accounted for in the unrestricted stopping powers. The stopping power ratio averaged over the primary electron spectrum is calculated using (Siebers et al. 2000).

$$S_{w,med} = \frac{\int_0^{E_{max}} (\Phi_E)_m (S/\rho)_w dE}{\int_0^{E_{max}} (\Phi_E)_m (S/\rho)_{med} dE}$$  \hspace{1cm} (III.9)

Where $(S/\rho)_w$ and $(S/\rho)_{med}$ are the unrestricted mass collision stopping power for the water and transport medium respectively, and $E_{max}$ is the maximum energy in the $(\Phi_E)_m$ distribution (NCRP-27 1961). To evaluate the Bragg-Gray stopping
power ratio for photon beams, knowledge of the electron fluence in the media is required. Presently, only MC based dose calculation algorithms are capable of determining this quantity. Equations III.8 and III.9 were used to convert absorbed dose to medium to absorbed dose to water for all MC based photon beam dose calculations.

<table>
<thead>
<tr>
<th>Material</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.119</td>
</tr>
<tr>
<td>Lung</td>
<td>0.998</td>
</tr>
<tr>
<td>Adipose</td>
<td>0.984</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.008</td>
</tr>
<tr>
<td>Bone1</td>
<td>1.012</td>
</tr>
<tr>
<td>Bone2</td>
<td>1.030</td>
</tr>
<tr>
<td>Bone3</td>
<td>1.047</td>
</tr>
<tr>
<td>Bone4</td>
<td>1.062</td>
</tr>
<tr>
<td>Bone5</td>
<td>1.077</td>
</tr>
<tr>
<td>Bone6</td>
<td>1.089</td>
</tr>
<tr>
<td>Bone7</td>
<td>1.101</td>
</tr>
<tr>
<td>Bone8</td>
<td>1.123</td>
</tr>
<tr>
<td>Bone9</td>
<td>1.134</td>
</tr>
<tr>
<td>Bone10</td>
<td>1.144</td>
</tr>
</tbody>
</table>
Figure III.11: Stopping power ratios: The graph shows the change of water-to-medium electron stopping power ratios with depth for several materials and how they vary with depth in water for a $10 \times 10$ cm$^2$ incident square field. A cut off energy for the track end term of 10 keV was used for all simulations. The MC uncertainty was less than 1\% for all simulations. Extracted from (Downes 2010).
CHAPTER IV

Organ motion, image guidance and dose escalation: Impact on RT

Uncertainties arising from a geometric perspective, with regard to delivering RT, stem from a variety of sources; for example, prostate delineation, patient setup, and organ motion. Organ motion can be categorised as either intra-fraction motion, occurring during radiation delivery, or inter-fraction motion, occurring between radiation treatments. The latter effect is clinically more significant (Langen and Jones 2001) and it is this uncertainty which is investigated further in this study. The uncertainty in knowing the position poses a problem as healthy tissue is required to be included in the PTV in order to achieve a desired level of TCP. This results in OARs inevitably being exposed to increased doses of radiation.

In September 2008, GUH introduced clinically an intra-modality 3D ultrasound (US) based IGRT system, Clarity™ (Elekta, Stockholm, Sweden) for prostate localisation. Images are acquired by both US and CT at the treatment planning stage. These images are aligned thus fixing the iso-center obtained from the CT data set with that obtained from the US data set. Subsequently, immediately
prior to each treatment fraction, a 3D US image is acquired. The 3D image is then aligned with the original US image. This yields displacement data in the right-left (RL), anterior-posterior (AP), and superior-inferior (SI) directions. The system does not correct for target rotation. Inter-fraction rotation of the prostate has been reported to be of the order of 3.7°, 1.1° and 1.9°, in the RL, AP and SI planes respectively (van Herk et al. 1995; Stroom et al. 1999). In order to provide a clear acoustic window, patients empty their bladder and consume 300 ml of water, 30 mins prior to each US scan. This enables reproducible bladder filling for each treatment fraction. Furthermore, patients are given a strict diet, in order to minimise major changes in anatomical position per fraction, due to solid and gaseous rectal filling. Major changes correspond to displacements greater than the PTV margin. The systems are calibrated to the corresponding CT and linac coordinate systems by means of a vendor supplied calibration phantom. The image guidance process is subject to rigorous quality assurance procedures as recommended by the manufacturer.

![Diagram](image.png)

**Figure IV.1:** Absolute iso-center shift for the prostate: The Clarity™ system provides daily couch shift data which give the required alignment between the pre-treatment position (the red circle) and its nominal treatment position (the blue circle) along the RL, AP, and SI directions.

A single case study of prostate localisation data was analysed using radiobiological models to evaluate the clinical effect of organ motion as a moderator in RT efficacy. The potential strength of IGRT is that it enables precise target localisation and therefore the possibility of margin reductions, thus decreasing the toxicity to normal tissue and improving the probability of complication free
treatment. With regard to the simulation process, the prostate was assumed to be a rigid structure (Arnesen et al. 2008) directly correlated in respect of organ motion with rigid OARs. Figure IV.2 depicts the inter-fraction organ motion simulated in this study. This motion is characteristic of displacements observed in GUH patients (Kleefeld et al. 2009), with 95% of LR displacements, 97% AP displacements, and 91% SI displacements falling within the bounds of the maximum and minimum displacements shown here for each plane.

**Figure IV.2:** Clinically observed inter-fraction organ motion for the prostate: This data enabled the absolute iso-center shifts for each fraction to be calculated. These displacements are representative of typical prostate displacements reported in GUH and are similar to those reported in previously published data (van Herk et al. 1995; Roeske et al. 1995; Rudat et al. 1996; Melian et al. 1997; Tinger et al. 1998; Antolak et al. 1998; Stroom et al. 1999; Zelefsky et al. 1999).

### IV.1 RT treatment model

The methodology for modelling the treatment process is based upon the simulation of RT delivered to a three dimensional rectilinear phantom, the dose distribution scored in the voxels of the phantom were used as input parameters for radiobiological models calculated in *MatLab*\textsuperscript{TM} (*MathWorks*, *Natick*, *Massachusetts*). The simulation process begins with the input parameters for
BEAMnrc, chosen to best replicate the linacs used in the RT department of GUH. The virtual linac produced by BEAMnrc was tuned so that the PDD and TDP curves produced were an accurate representation of the clinical 6 MeV photon beams used in GUH. The outputted phase-space file obtained from this stage of the simulation was then used as an input file for DOSXYZnrc (Kawrakow and Walters 2006). The use of such simple geometries was chosen to eliminate anatomical confounding factors, the structures are reasoned to be generically representative of the structures of interest, as opposed to any given individual patients’ specific anatomical geometry. Similar to the medical internal radiation dose formalism (Loevinger and Berman 1968). The dimensions of the phantom were designed to approximate those of the average male abdomen, $30 \times 30 \times 25$ cm$^3$ (X,Y,Z) - (RL,SI,AP). Each phantom voxel had a volume of $1 \times 10^{-3}$ cm$^3$, enabling dose resolution of up to 1 mm in the X,Y, and Z planes. A six field prostate treatment, equivalent to those used clinically at GUH, was delivered to the phantom and the subsequent dose values were scored by DOSXYZnrc into each phantom voxel. The phantom was located at a distance of 100 cm source to iso-center distance for the six beams. The density of the majority of voxels was set to that of water (1 g/cm$^3$), the presence of bone (1.6 g/cm$^3$) in the form of the femoral heads was included in the simulation. The dose distribution produced in the phantom was used to create a three dimensional dose distribution matrix. This matrix was converted to physically meaningful dose values, as opposed to the statistical values outputted by DOSXYZnrc, see Chapter III.

Inside the phantom dose distribution matrix, a cubic matrix, representative of a prostate or OAR could be designed. Three matrices were designed at iso-center as tumours. This allowed the calculation of three prostate cases: small, medium and large. Corresponding appropriate cubic matrices for the bladder, rectum and femoral heads were designed for each of the prostates, see Table IV.1. These values are consistent with clinical values observed in GUH. A distance of 0.6 cm and 0.1 cm was maintained between the bladder-prostate interface and the rectum-prostate interface, respectively. Each prostate was treated with ultra conformal
Organ motion, image guidance and dose escalation: Impact on RT

**Figure IV.3**: Monte Carlo percentage depth dose curves: The left graph shows the tuned MC simulation overlaid on QA measurements as a benchmark. The right graph shows the impact of the inclusion of bone within the simulation. The effects of inhomogeneity can be seen in: i) the changes in secondary electron fluence at the boundaries of the femoral head. ii) The dose to the femoral head is slightly less, further downstream of the femoral head the dose is reduced due to the shielding effect of the bone, caused by the higher electron density.

**Figure IV.4**: Treatment setup for the rectilinear phantom: The red cube represents the prostate. The purple, gold, and green cubes represent the rectum, bladder and femoral heads respectively. The treatment beams delivered at $0^\circ$, $45^\circ$, $115^\circ$, $180^\circ$, $225^\circ$, and $315^\circ$.

Radiotherapy (UCRT) and CRT. The PTV margin around the prostate for CRT case was defined as 1 cm, where as for the UCRT case the PTV margin around the prostate was defined as 0.5 cm. The PTV margin on the posterior side of the prostate was reduced by 30% in order to spare the rectum unnecessary irradiation. In relation to the simulation of organ motion within the phantom, the clinically observed data was directly converted to voxel shifts of the same
magnitude within the phantom.

**Figure IV.5**: Prostate volumes measured at GUH: The bar chart on the left shows measured prostate volumes of 25 patients. The histogram on the right reveals this data to be approximately Gaussian, passing the Shapiro-Wilk test for Normality: $P = 0.14$, $W$ Statistic = 0.89, at a significance Level = 0.05. This enabled the calculation of the three prostate cases, small, medium, and large, to the nearest cube root, based on the $Mean \pm SD$.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Small</th>
<th>Medium</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>15.63 cm$^3$</td>
<td>35.94 cm$^3$</td>
<td>50.65 cm$^3$</td>
</tr>
<tr>
<td>Bladder</td>
<td>19.68 cm$^3$</td>
<td>46.66 cm$^3$</td>
<td>64.00 cm$^3$</td>
</tr>
<tr>
<td>Rectum</td>
<td>25.80 cm$^3$</td>
<td>58.08 cm$^3$</td>
<td>81.25 cm$^3$</td>
</tr>
<tr>
<td>Femoral head</td>
<td>9.26 cm$^3$</td>
<td>21.95 cm$^3$</td>
<td>29.79 cm$^3$</td>
</tr>
</tbody>
</table>

The three prostate dose matrices produced from the BEAMnrc/DOSXYZnrc simulations, with appropriate radiobiological parameters applied to each element, coupled with the clinically observed organ motion, enabled the biological evaluation of the treatment regimes. This was done under UCRT and CRT, guided and unguided, conventional and escalated dose for the three different prostate volumes, in order to assess the effects of each of the various factors involved in the modelling process and therefore determine which treatment is optimised to yield the best possible outcome.

The prostate was defined to have either static or dynamic motion relative to the iso-center of the beam during treatment, and the prescription dose was either of a conventional magnitude or escalated to the limits of GUH dose constraints.
Image guidance insured that the prostate was static relative to the iso-center of the beam per fraction during treatment, the absence of image guidance resulted in the prostate being displaced from the iso-center of the beam per fraction, and therefore dynamic. The bladder and rectum also follow this convention. The femoral heads however, are the exact opposite, and would be considered dynamic relative to the iso-center of the beam under image guided treatment, and static in the absence of image guidance.

**Figure IV.6:** Radiotherapy scenarios modelled: A flow chart describing the scenarios modelled for this study.

The treatment plans complied with the dose volume constraints employed in GUH, displayed in Table IV.2.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Dose</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV (Prostate)</td>
<td>70.3 Gy</td>
<td>100%</td>
</tr>
<tr>
<td>Femoral head</td>
<td>50.0 Gy</td>
<td>≤50%</td>
</tr>
<tr>
<td>Bladder</td>
<td>70.0 Gy</td>
<td>≤20%</td>
</tr>
<tr>
<td>Rectum</td>
<td>40.0 Gy</td>
<td>≤60%</td>
</tr>
<tr>
<td></td>
<td>45.0 Gy</td>
<td>≤50%</td>
</tr>
<tr>
<td></td>
<td>60.0 Gy</td>
<td>≤40%</td>
</tr>
<tr>
<td></td>
<td>70.0 Gy</td>
<td>≤20%</td>
</tr>
<tr>
<td></td>
<td>75.6 Gy</td>
<td>≤15%</td>
</tr>
<tr>
<td></td>
<td>79.0 Gy</td>
<td>≤5%</td>
</tr>
</tbody>
</table>
Figure IV.7: Dose distribution in the rectilinear phantom: The treatment beams were weighted to deliver 2 Gy to the iso-center of the phantom. The green cube represents the prostate. The purple, gold, and black cubes represent the rectum, bladder and femoral heads respectively. The small patient is depicted here. Images (A)-(D) show CRT treatment and images (E)-(H) show UCRT treatment.
IV.2 Results of the RT treatment model

**Figure IV.8**: DVH data for CRT (i) and UCRT (ii): Of static and dynamic organ motion for a conventional prescription dose. The DVH data shows that the current margins employed in CRT are sufficient to ensure that unguided treatment results in an almost identical dose curve for the CTV as guided treatment. The data also displays the overall trend of the bladder moving out of the treatment field and the rectum moving into the treatment field. The DVH data also reveals that the margins utilised in UCRT are insufficient to ensure that unguided treatment will result in an acceptable dose curve for the CTV. However, the guided UCRT treatment does deliver a satisfactory dose curve for the CTV. Finally, as is to be expected, the DVH data demonstrates the overall sparing of the bladder and rectum due to the reduced margins.
Figure IV.9: Treatment data for unguided conventional CRT and UCRT: (A) TCP treatment data for unguided conventional CRT and UCRT. These bar charts show a significant deterioration in TCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy without image guidance, a mean loss of 20.0% is calculated for ∆TCP. (B) NTCP Rectum treatment data for unguided conventional CRT and UCRT. These bar charts show a small improvement in NTCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy without image guidance, a mean loss of 3.2% is calculated for ∆NTCP. (C) UTCP treatment data for unguided conventional CRT and UCRT. These bar charts show a significant deterioration in UTCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy without image guidance, a mean loss of 17.0% is calculated for ∆UTCP.
Figure IV.10: Treatment data for guided conventional CRT and UCRT: (A) TCP treatment data for guided conventional CRT and UCRT. These bar charts show a slight decline in TCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean loss of 0.7% is calculated for $\Delta TCP$. (B) NTCP treatment data for guided conventional CRT and UCRT. These bar charts show a small improvement in NTCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean loss of 3.1% is calculated for $\Delta NTCP$. (C) UTCP treatment data for guided conventional CRT and UCRT. These bar charts show a minor improvement in UTCP for UCRT compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean gain of 1.8% is calculated for $\Delta UTCP$. 
Figure IV.11: DVH data for UCRT: Of static and dynamic organ motion for an escalated prescription dose. The DVH data shows the sizeable gains that can be made in the dose delivered to the CTV, whilst still abiding by GUH dose constraints, through guided UCRT dose escalated treatment. The DVH data also reveals that it is the femoral head which is the dose limiting organ in this instance.
These findings are for a treatment regime of 2 Gy per fraction. The DVH data for the large and small patients expressed the same properties as the medium patient DVH data, and are omitted for brevity. NB: The NTCP of the bladder and femoral heads for all volume sizes for both UCRT and CRT with and without image guidance was 0% and 0.2% respectively.

**Figure IV.12:** Treatment data for guided dose escalated CRT and UCRT: (A) TCP treatment data for guided conventional dose CRT and escalated dose UCRT. These bar charts show a significant increase in TCP for UCRT with a mean escalated prescription dose of 86 Gy compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean gain of 16.7% is calculated for $\Delta TCP$. (B) NTCP Rectum and Femur treatment data for guided conventional dose CRT and dose escalated UCRT. These bar charts show a slight increase in the NTCP-Rectum for UCRT with a mean escalated prescription dose of 86 Gy compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean gain of 0.1% is calculated for $\Delta NTCP$. (C) NTCP Femur treatment data for guided conventional dose CRT and dose escalated UCRT. These bar charts show a drastic rise in the NTCP-Femur for UCRT with a mean escalated prescription dose of 86 Gy compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean gain of 2.6% is calculated for $\Delta NTCP$. (D) UTCP treatment data for guided conventional dose CRT and dose escalated UCRT. These bar charts show a significant increase in UTCP for UCRT with a mean escalated prescription dose of 86 Gy compared with CRT for a conventional prescription dose of 74 Gy with image guidance, a mean gain of 13.5% is calculated for $\Delta UTCP$. 
IV.3 Discussion of the RT treatment model

The emphasis in this current work was on investigating the effects of margin reduction in the presence of organ motion for both guided and unguided treatment. The results of this lead us to examine the role of dose escalation for image guided UCRT. The results show that, with respect to unguided CRT, there is a minor improvement with image guided CRT. Additionally, there is a small improvement with image guided UCRT. Finally, there is a significant improvement with dose escalated image guided UCRT. The guided CRT plan UTCP of 79.5% holds virtually constant at 79.3% in the case of the unguided CRT plan, with a decrease in the $\Delta UTCP$ of 0.2%. The guided UCRT plan UTCP of 78.7% plummets to 59.4% in the case of the unguided UCRT plan, with a decrease in the $\Delta UTCP$ of 19.3%. The guided UCRT dose escalated plan UTCP of 96.2% dramatically out performs the 79.5% in the case of the guided CRT conventional dose plan, resulting in an increase of 16.7% in the $\Delta UTCP$. The immediate findings of this simulation are confined to the six field setup, and other beam configurations, such as IMRT, or five field techniques currently in use elsewhere clinically as the standard prostate setup, may give different results. The organ motion was characteristic of displacements observed in GUH patients, however the motion was rigid in nature, deformation would be more accurate. The cubic geometric arrangement of the treatment setup together with the predominately posterior motion of the organs, depicted in the DVHs, the bladder moves into the beams while the rectum moves out, may have lead to spurious results in relation to the absolute values of the metrics used, this does not undermine the relative values of the metrics used in determining whether one treatment was superior to another. Consequently these findings require confirmation in clinical DICOM-RT data sets. The TCP model has been well validated in this study, see Chapter II. However, some added caution should be exercised in the use of the LKB NTCP model, despite being accepted as the most appropriate NTCP model for the analysis and evaluation of external beam RT plans, the LKB NTCP most likely overestimates the complication rate witnessed in the rectum. A clinical
study conducted by (Rancati et al. 2004) reported NTCP rates of 1.6% from a cohort of 547 patients treated up to a total dose of 79.2 Gy. The LKB NTCP model in this study predicts an average risk of 4% for rectal injury from a total dose of 74 Gy. These radiobiological models were used to calculate the biological outcomes for the prostate, bladder, rectum and femoral heads in the context of large, medium and small volume scenarios. The results suggest that there is potentially a greater gain to be achieved from guided UCRT dose escalated plans for large volumes than there is for small volumes. The volume effect seen here with regard to TCP, larger tumour volume corresponded with smaller TCP values. The inverse was true for the volume effect seen here with regard to NTCP, smaller OAR volumes corresponded with larger NTCP values. This trend due to the volume effect is in agreement with the findings of previous studies (Bentzen and Thames 1996; Bentzen et al. 2010; Michalski et al. 2010). The NTCP values predicted for the bladder and femoral heads for all volume sizes for both UCRT and CRT with and without image guidance was 0% and 0.2% respectively, this is in agreement with the findings of previous studies (Viswanathan et al. 2010; Marks et al. 2010).
IV.4 Conclusions of the RT treatment model

Margin reduction is advised

The present work illustrates the radiobiological effect of three different treatment strategies, namely guided or unguided, UCRT or CRT, and conventional or escalated. The optimal margins of treatment delivery under UCRT and CRT in the instance of both guided and unguided treatment were simulated and analysed. Geometric uncertainties relating to clinically observed organ motion, by way of the ClarityTM system, were accounted for in the simulation and modelling process in the form of a cubic phantom containing a cubic CTV and OARs, and thus the end point radiobiological effect was evaluated for various biological factors. The simulation and modelling process found that the optimal treatment margins for the delivery of RT treatment, are, as expected, those utilised in UCRT guided treatment. The simulation and modelling process also highlighted that the inherent benefits of margin reduction in UCRT are directly linked to grave consequences if target coverage during treatment is compromised. The use of UCRT is advocated only on the basis, that IGRT is employed, so that treatment delivery per fraction can guarantee target coverage. Thus, the emphasis here is to optimise the geometry which can be used with confidence clinically, as is the case with current conventional CRT. The results clearly show that in order to reap the full benefits of guided UCRT, dose escalation is required.

A summary of the preliminary conclusions which can be drawn from the beam model data:

1. For the majority of patients there is no discernible difference between guided and unguided CRT. This has clinical as well as economic implications for RT departments.

2. In order to optimise IGRT, margin reduction is required.
3. To implement margin reduction, imaging for each fraction is required.

4. In order to make optimal use of IGRT and margin reduction, dose escalation is required.

These findings advocate, that in RT centres where IGRT is available, margin reduction for clinical RT treatment be implemented in order to optimise the innate benefits of IGRT. The findings also advocate that dose escalation, to OAR constraints in conjunction with image guidance and margin reduction, be considered. A natural prudent approach for the future implementation of these findings would be a gradual phased introduction of dose escalation in conjunction with image guidance and margin reduction, with continuous clinical review.
Simulation of organ deformation in RT

Roan Havelin is gratefully acknowledged for his contribution to this section of the thesis.

V.1 The programming language

Matlab\textsuperscript{TM} is a high-performance language for technical computing which integrates computation, visualisation, and programming in an easy to use environment where problems and solutions are expressed in familiar mathematical notation. Like most other programming languages, the MatLab\textsuperscript{TM} language provides mathematical expressions, but unlike most programming languages, these expressions involve entire matrices. These variables are stratified into different classes.

- Numeric arrays: Integer and floating-point data stored as a matrix
- String arrays: Characters and arrays of characters
- Structures arrays: Data of varying types and sizes stored in fields of a structure
V.2 Processing DICOM-RT files

The DICOM-RT file format is a binary format with metadata at the start of the file. The metadata is made up of a number of data elements. Each data element contains four fields: a data element tag, a value representation, a value length and a value field. The metadata describes the DICOM file type and the type of information contained in the rest of the file (Riddle and Pickens 2005). It is this information that must be edited in order to simulate organ deformation.

There are a large number of software packages that can process DICOM files for viewing, editing, or for file transfer. The well known and versatile toolbox packages for MatLab™ that allow DICOM files to be read in, viewed, and edited, 'DICOM-RT' and 'Image-processing' were utilised in this work.

**Figure V.1:** DICOM-RT file explored: The data contained within the DICOM-RT file is imported into the MatLab™ workspace for viewing and editing. The images displayed here show the directory structure within the DICOM-RT file. The arrows move through the DICOM-RT file hierarchy to present the values assigned to the first contour level of the first structure.
The verification of RT plans is an essential step in the treatment planning process. This is especially important for CRT and IMRT plans which produce complex 3D dose distributions. The deformation code was developed to allow inter-fraction organ motion to be incorporated easily into RT treatment plans.

V.3 The deformation code

The deformation code offers the ability to dynamically account for inter-fraction organ motion in treatment planning, facilitating a fraction by fraction evolutionary approach to treatment planning on an independent platform. The deformation code is composed of a set of functions written in the *MatLab*™ scientific software environment and is based on *MatLab*™ low level functions which support the standard format for DICOM and its RT extension DICOM-RT. The deformation code provides a set of routines to import, process, and deform RT structures. The first step in analysing the DICOM-RT data is to import it into the *MatLab*™ workspace. The workspace consists of the set of variables built up during a session of *MatLab*™ and stored in memory. The DICOM-RT file is imported using the function `Info = dicominfo(DICOM-RT)` which reads the metadata and images from the DICOM-RT file specified. The next step is to extract the contour points from the info structure array in the workspace. This is done by generating a string array to index the content from the info structure array. Each organ of interest, in this instance, the prostate, rectum, and bladder is identified within the info structure array and defined appropriately as a numeric array in the *MatLab*™ workspace. This numeric array contains the (X,Y,Z) Cartesian co-ordinates of the contour points, where X is equivalent to RL, Y is equivalent to AP, and Z is equivalent to SI. To verify that each organ has been imported and stored correctly, the organs can be displayed as a set of contour lines which span several planes. The location of these planes match the Z location of the acquired CT slices.

---

1 Colour key: Colours indicate a Variable, a Function, and a File
Once successful import of the organs has been verified, the next step is to convert the contours to vertices. The conversion to vertices is necessary to build a finite element structure which can be deformed. The initial step in this process is to declare an n-by-n-by-m construct matrix of zeros for each organ, n must be large enough to house the maximum and minimum values in the RL and AP planes contained within the organs. The number of levels in the SI plane for the organ determines the value of m. Next, the indices values from the construct matrix are correlated with the organ contours and used to create a 3D binary array. The organ contours are used to produce a surface of ones in the construct matrix, the volume inside is filled with ones also. The penultimate step in this process is to reduce the number of vertices generated, this is done by deleting all vertices that are within a distance of 3 mm from any other vertex within each organ. In this way, a 3 mm × 3 mm × 3 mm grid system that is equivalent to the voxel resolution of the of the treatment plan is established. This reduction in vertices improves computational efficiency, as no time is exhausted computing the movement of superfluous vertices. The final step, if required, in preparing the organs for deformation is that an overlap of vertices from different organs is removed from the respective numeric arrays.
The prostate is deemed to be the principal organ with all other organs subordinate to it. As a consequence, all vertices within a distance of 3 mm from the exterior vertices of the prostate are deleted. This circumvents the physically impossible situation of an overlap of vertices within different organs, thus ensuring geometrical sovereignty of each organ. The organs now have a finite element structure and are ready to be deformed. Organ volume is not conserved during deformation, this is in keeping with clinical observation (Roeske et al. 1995; Melian et al. 1997; Tinger et al. 1998; Zelefsky et al. 1999). In order to deform the organs a numeric array containing the inter-fraction displacement data must be created. This numeric array holds data for the RL, AP, and SI displacements of each fraction for all 37 fractions of the treatment. The contents of this array are used as input parameters for the deformation function, \texttt{deformation}(GTV, OARs, Elasticity, Displacement, Iterations, Grid, Graph). The deform function begins by ascertaining which vertices belong to the moving organ, GTV, and which vertices belong to the deformable organs, OARs. The function also establishes all the possible connections between all the vertices within each organ, as well as the number of iterations required to advance the deformation simulation to the end of the displacement. In order to decrease computation time pre-allocation of the vertices is performed.
Figure V.4: Organs converted to a finite element structure: The conversion from contours to vertices is necessary to build a finite element structure which can be deformed. The prostate is shown here as blue vertices, while the rectum and bladder are shown here as red vertices.

The initial vertices structure of each of the organs is declared in a numeric array. The moving vertices are declared in another numeric array and finally the vertices to be deformed are also declared in another numeric array. The number of vertices which can be deformed by each individual vertex is defined as All near connections. The near connections limit the distance by which each vertex can influence other vertices. This effectively creates, for each vertex, a local region within an organ for deformation and thus speeds up computation time.

The deformation simulation begins by computing the deformation effects of the first iteration of the simulation and the algorithm is executed as follows. The moving organ, the prostate in this instance, is defined to be perfectly rigid and moves along a vector path calculated from the displacement array. The first iteration displaces the prostate by a fraction of the total displacement. The immediate vertices surrounding the prostate will experience either an attractive or repulsive force depending upon the orientation of the OARs and the vector displacement of the prostate. Each of the immediate vertices will be displaced by the amount the prostate moves per iterative step. The elastic limit will then
modulate the displacement by which these vertices move. These vertices in turn will then affect the next nearest surface of vertices. This effect will propagate outwards through each structure. This entire process is repeated iteratively until the end of the displacement.

Figure V.5: Conservation of Pythagoras: Illustrates the concept of the COP algorithm. As a deformation force is applied, points $p_1$ and $p_2$ move to $p_1'$ and $p_2'$, conserving the hypotenuse length from a triangle structure derived from the two points. This process is repeated for each vertex in each RT structure set.

The following equation describes the geometric translation experienced by each vertex in each RT structure over $n$ iterations.

\[
\begin{align*}
X'_{n} &= X_n + X_{Movement} = X_n + q \times (r \cos(\phi') \cos(\theta')) \\
Y'_{n} &= Y_n + Y_{Movement} = Y_n + q \times (r \cos(\phi') \sin(\theta')) \\
Z'_{n} &= Z_n + Z_{Movement} = Z_n + q \times (r \sin(\phi'))
\end{align*}
\]  

(V.1)

Here $X$, $Y$, and $Z$ are the co-ordinate positions in space, $r$ is the original hypotenuse, $\phi'$ and $\theta'$ are the elevation and azimuth angular displacements in radians measured from the positive x-axis, and the xy-plane. Finally $q$ is a constant, Elasticity, with a value between 0 and 1. $q$ is used to describe the movement of
one structure in relation to the movement of another structure, 1 resulting in a perfectly rigid movement, and 0 resulting in no movement. A value for $q > 0$ and $< 1$ results in a deformed movement. The deformation code mimics known anatomical changes through appropriate compression and expansion of the OARs.

The results of the deformation are plotted to ensure that the outcome is proper.

![The finite element structure deformed](image)

**Figure V.6:** The finite element structure deformed: The prostate has been displaced and as a consequence has deformed both the rectum and bladder. The prostate is shown as blue vertices, while the rectum and bladder are shown as red vertices here.

Now that deformation of the organs has been performed successfully, the next step is to generate contour points from the vertices’ numeric array in the workspace. Each vertex is rounded to the CT grid positions. A contouring algorithm determines the outer vertices on the RL-AP plane at each level on the SI axis for each organ. A linear interpolation is performed between the vertices to produce the contours. To ensure geometrical sovereignty of each organ, all contours are subject to a polygon set operation utilising region subtraction. This avoids the situation of an overlap of different organ contours within the DICOM-RT file.

The penultimate step is to extract the newly deformed contour points from the numeric arrays created in the workspace and write them into the appropriate
fields in the info structure array. This is done by generating a string array to index the content from the info structure array. Each organ of interest, in this case, the prostate, rectum, and bladder, are identified within the info structure array and replaced with the newly deformed contour numeric arrays from the MatLab™ workspace.

The final step in this process is to write the data contained within the info structure array into a new DICOM-RT file. This is done by using the function

\[
\text{DICOM-RT\_deformed} = \text{dicomwrite}(\text{Info, DICOM-RT})
\]

which copies the metadata and images from the Info structure array into the new DICOM-RT file specified, DICOM-RT\_deformed.

V.4 The deformation code applied

The deformation model was applied to a DICOM-RT file of a patient treated in GUH under image guidance. The deformation was based on inter-fraction organ motion data recorded by the Clarity™ system. Figures V.8, V.9 and V.10 show the results of the deformation model on the contour sets of the bladder, rectum and prostate, respectfully.
Figure V.8: Bladder contour - Original and Deformed: A 3D volume rendering of the bladder, the original and deformed structures are depicted in green and black respectively. The motion of the prostate has been largely posterior in this instance, allowing the bladder to fill the space vacated.

Figure V.9: Rectum contour - Original and Deformed: A 3D volume rendering of the rectum, the original and deformed structures are depicted in red and black respectively. The motion of the prostate has been largely posterior in this instance, forcing the rectum to compress.
Figure V.10: Prostate contour - Original and Deformed: A 3D volume rendering of the rectum, the original and deformed structures are depicted in blue and black respectively. The motion of the prostate has been largely posterior in this instance, the prostate is treated as perfectly rigid structure and is undeformed in translation.

Figure V.11: RT contours - Original and Deformed: A 3D volume rendering of the bladder, rectum, prostate and femoral heads. The image shows the deformed RT structures along with an iso-volume of 95% of the prescribed dose. The original prostate is superimposed (white) to give some perspective.
Simulation of organ deformation in RT

Figure V.12: DICOM image contours - Original and Deformed: A transverse CT slice of a patient showing the bladder, rectum, femoral heads and prostate before (A) and after (B) deformation has been simulated. The bladder, rectum, prostate and femoral heads are outlined in black. The image shows the RT structures within isodose curves of 30% (dark blue line), 50% & 70% (light blue lines) and 95% (red line) of the prescribed dose. The motion of the prostate has been largely posterior in this instance, forcing the rectum to compress and allowing the bladder to expand.
Figure V.13: DICOM image contours - Original and Deformed: A transverse CT slice of a patient showing the bladder, rectum, femoral heads and prostate. The bladder, rectum, prostate and femoral heads outlined in black are the contours after deformation has been applied. The prostate outlined in blue is the contour before deformation has been applied. The image shows the RT structures within iso-dose curves of 50% (light blue line), 80% (green line) and 95% (red line) of the prescribed dose. The motion of the prostate has been largely posterior in this instance, forcing the rectum to compress and allowing the bladder to expand.
Figure V.14: DICOM image contours - Original and Deformed: Sagittal and coronal CT slices of a patient showing the bladder, rectum, femoral heads and prostate. The bladder, rectum, prostate and femoral heads outlined in black are the contours after deformation has been applied. The prostate outlined in blue is the contour before deformation has been applied. The image shows the RT structures within iso-dose curves of 50% (light blue line), 80% (green line) and 95% (red line) of the prescribed dose. The motion of the prostate has been largely posterior in this instance, forcing the rectum to compress and allowing the bladder to expand.
V.5 Discussion of the deformation code

In this work, the deformation of RT-structures was performed through finite element simulation. The theory of deformation between linear-elastic bodies with simple geometries can be applied to describe deformation, in this instance for the clinical case of the prostate, bladder and rectum. An elastic sphere, analogous to the prostate, of radius $R$ deforms an elastic half-space, analogous to the bladder or rectum, by a distance $D$. The applied force $F$ is related to the displacement by (Popov 2010).

$$F = \frac{4}{3} E^* R^{1/2} D^{3/2}$$  \hspace{1cm} (V.2)

where

$$E^* = \frac{E}{1 - \nu^2}$$  \hspace{1cm} (V.3)

Here $E$ is the elastic modulus and $\nu$ is the Poisson ratio. Equations V.2 and V.3 were used to calculate deformation displacements based upon experimental values obtained from the literature (Krouskop et al. 1998; Levantal et al. 2006; Choi and Zheng 2005; Wang et al. 2008). The elastic modulus of soft tissue was taken to be 87 kPa (Krouskop et al. 1998) assuming a 9:1 ratio of cancerous and healthy tissues, see equation II.9. An elastic modulus of 87 kPa is within the range of credible values (Levantal et al. 2006). The Poisson ratio can be reasonably assumed to be 0.4 (Choi and Zheng 2005). Pressure values in the bladder vary between 100 kPa and 150 kPa (Wang et al. 2008) similar values can be assumed for the rectum. The contact area expected between the prostate and the structure experiencing deformation can realistically be expected to be of the order of $3.14 \times 10^{-4}$ m$^2$. Based upon the accepted range of pressure values found within the bladder, an applied force range of approximately 30 – 50 N can be exerted on the prostate. Using equation V.2 the expected range of
deformation displacements can be calculated. The resulting range of potential deformation displacements are between 12 – 17 mm. This is in agreement with clinical measurements performed in GUH. A graph of applied force, deformation displacement and pressure is shown in Figure V.15. The slope of this graph with respect to applied force and deformation displacement produces a spring constant, $k$, determined from Hooke’s law, described by equation V.4.

$$F = kS$$  \hspace{1cm} (V.4)

Here $S$ is the displacement of the spring from its equilibrium position, $F$ is the applied force required to displaced the spring from its equilibrium position and $k$ is a constant known as the spring constant.

![Hooke's Law](image)

**Figure V.15:** Predicted deformation displacements: The increase in pressure produces an increase in the applied force and therefore the deformation displacement also increases. The slope of the curve, $R^2 = 0.999$, with respect to the applied force and the deformation displacement is a spring constant with a value of $3976 \text{ N m}^{-1}$. This is similar to a value of $5000 \text{ N m}^{-1}$ reported in the literature for fascicle and ligament tissue (Doi et al. 2006).
Hooke's law of elasticity states that the linear deformation of a spring is directly proportional to the applied force. Several materials, including biological materials, obey Hooke’s law, provided that the applied force does not exceed the material’s elastic limit. Materials for which Hooke’s law is appropriate are known as linear-elastic materials. The constant $q$ used in equation V.1 was always assumed to be 0.8. The physical explanation of this $q$ value is that for each inter-fraction deformation simulated, the applied force is always assumed to be 80% of what is required to deform each vertex of the OARs by the total displacement recorded by the *Clarity*™ system. A $q$ value of 1 results in a perfectly rigid movement of the deforming vertices, and a $q$ value of 0 results in no movement of the vertices. This mathematical framework arises from the inverse nature of the deformation problem, the prostate displacements are known but the pressures and applied forces to the prostate, bladder and rectum are not. A $q$ value equal to 0.8 was obtained heuristically through iterative simulation of organ deformation. This value for $q$ was deemed to produce realistic and recognisable anatomical changes through suitable compression and expansion of the OARs, see Figures V.8, V.9, V.10, V.11, V.12, V.13, V.14 and V.17, using a plausible bio-physical input parameter, see Figure V.15. This value for $q$ may be somewhat arbitrary in nature; nevertheless, it does result in credible deformation forces for each inter-fraction deformation. Accurate measurements of the forces applied to the prostate, bladder and rectum are required to eliminate this assumption for the $q$ value from the deformation code. See figures V.18 and V.19 for an assessment of the influence of the $q$ value on the absolute volume change experienced by the RT-structures of patient(1).

Figure V.16 contains a histogram of AP prostate displacements produced by the deformation code, overlaid upon another histogram of AP prostate displacements produced by the US measurement of the *Clarity*™ system. The histograms produce similar fitted Gaussian curves. The deformation code successfully produces realistic and recognisable organ deformation, based upon inter-fraction prostate displacement data, using bio-physically credible input parameters.
Figure V.16: Simulated and measured AP prostate displacements: The graph displays two histograms of patient prostate displacements in the AP direction. The dark grey bars represent the prostate displacements measured by the Clarity™ system and the light grey bars represent the simulated prostate displacements produced by equations V.2 and V.3. The displacements are based upon a mean pressure of 125 kPa with a standard deviation of 25 kPa and encompassed the full range of displacement scenarios, such as full bladder/empty rectum and empty bladder/full rectum. Each distribution has a sample size of 2072, equivalent to 37 fractions for 56 patients. The distributions produce overlying fitted Gaussian curves with constant variance, failing the Shapiro-Wilk test for Normality: $P = 0.0003$, $R^2 = 0.96$, $W$ Statistic = 0.87, at a significance Level = 0.05 for the US measurements and $P = 0.0055$, $R^2 = 0.98$, $W$ Statistic = 0.95, at a significance Level = 0.05 for the deformation simulation.
Figure V.17: DICOM image contours - Original and Deformed: Transverse, coronal and sagittal CT slices of a patient showing the prostate, bladder and rectum and before (a,c,e) and after (b,d,f) deformation has been simulated. The prostate, bladder and rectum are outlined in white. The image shows the RT-structures within iso-dose curves of 30% (dark blue line), 50% & 70% (light blue lines) and 95% (red line) of the prescribed dose. The motion of the prostate has been largely posterior in this instance, forcing the rectum to compress and allowing the bladder to expand.
Figure V.18: RT-structure volume changes: The graphs display the absolute volume changes in both the rectum and bladder, during compressive (Top) and expansive (Bottom) prostate displacements of ±(5,5,5) mm, for various $q$ values. The absolute volume of the prostate, bladder and rectum is 32 cc, 133 cc and 76 cc, respectively. A moderate change in absolute volume of the bladder and rectum is predicted for these prostate displacements, there is no change in the volume of the prostate. The graphs show a larger range in volume change in the expansive scenario when compared to the compressive scenario. The rectum exhibits a greater sensitivity to the choice of $q$ value than the bladder with a greater range in absolute volume change for both prostate displacement scenarios. These results are subjective to the anatomy of patient(1) and the prostate displacement vector.
Figure V.19: RT-structure volume changes: The graphs display the absolute volume changes in both the rectum and bladder, during compressive (Top) and expansive (Bottom) prostate displacements of $\pm (10,10,10)$ mm, for various $q$ values. The absolute volume of the prostate, bladder and rectum is 32 cc, 133 cc and 76 cc, respectively. A sizeable change in absolute volume of the bladder and rectum is predicted for these prostate displacements, there is no change in the volume of the prostate. The graphs show a larger range in volume change in the expansive scenario when compared to the compressive scenario. The rectum exhibits a greater sensitivity to the choice of $q$ value than the bladder with a greater range in absolute volume change for both prostate displacement scenarios. These results are subjective to the anatomy of patient(1) and the prostate displacement vector.
CHAPTER VI

Improved quantification of IGRT treatment of the prostate

Inter-fraction organ motion is a well known problem in RT (van Herk et al. 1995; Roeske et al. 1995; Rudat et al. 1996; Melian et al. 1997; Tinger et al. 1998; Antolak et al. 1998; Stroom et al. 1999; Zelefsky et al. 1999; Fraser et al. 2010; Barrett et al. 2008) as anatomical changes in the path of treatment beams have been shown to alter the dose distribution throughout RT treatment (Happersett et al. 2003; Lujan et al. 2003; Miralbell et al. 2003; Schaly et al. 2004; Stroom et al. 2000). Traditionally, the PTV is used to manage this problem. The PTV is a geometrical concept, which takes into consideration the net effect of all the possible geometrical variations and inaccuracies so that adequate coverage of the CTV is achieved, and thus ensures that the prescribed dose is delivered to the CTV (ICRU 1993, 1999). The CTV is designed to incorporate sub-clinical disease around the tumour, which is known as the GTV (McGarry et al. 2009). Delineation of the CTV for prostate cancer is presently based on the clinical likelihood of extra-capsular extension and involvement of the seminal vesicles as a function of tumour characteristics, i.e. stage and PSA level (Tinger et al. 1998). Numerous studies have investigated and described methods for developing PTV margins to account for random and systematic changes during the course of RT
Improved quantification of IGRT treatment of the prostate
treatment (van Herk et al. 2000; Stroom et al. 1999; McGarry et al. 2009; Hooge-
man et al. 2005; Redpath and Muren 2005). It has been shown that for "realistic"
prostate geometrical uncertainties, a PTV margins of 12 mm is required in order
to guarantee that 90% of the patient population receive at least 95% of the pre-
scribed dose in the CTV (van Herk et al. 2000). Such large margins inevitably
contribute to complication of the OARs. More modern methods employ image
guidance to further enhance the management of this uncertainty. Precise knowl-
edge of the CTV location immediately prior to treatment is essential for safe and
accurate margin reduction. Pinpointing the CTV at the time of treatment is the
purpose of IGRT (Johnston et al. 2008).

VI.1 Image guidance

The purpose of image guidance is to provide accurate daily localisation of the
CTV, in this case the prostate, so that the prescribed treatment for the patient
may be delivered as planned. In IGRT patients are typically repositioned at iso-
center immediately prior to each treatment fraction, thus ensuring that adequate
target coverage is achieved. However, repositioning the patient to better align the
prostate with the linear accelerator’s iso-center invariably results in the treatment
beams passing through a different patient geometry than planned. Potentially
compromising the delivery of the prescribed therapeutic dose. Furthermore, the
structure of the OARs will also now be different than planned due to organ de-
formation effects associated with inter-fraction organ motion. In the case of the
prostate, dynamic physiological processes lead to deformation of the bladder and
rectum. Nevertheless, dose recalculation and radiobiological modelling are not
routinely performed in RT centres to assess the dosimetric and clinical conse-
quences of these effects.

There are three scenarios to consider with regard to inter-fraction organ motion
and deformation.
• The original treatment without deformation.

• The unguided treatment with deformation.

• The guided treatment with deformation.

The original treatment is the planned treatment, depicted in scenario (a) of figure VI.1. Unguided treatment, depicted in scenario (b) of figure VI.1, results in the dose distribution being blurred and distorted relative to the planned distribution due to inter-fraction organ motion and deformation. Correcting for organ motion with guided treatment, depicted in scenario (c) of Figure VI.1, results in the dose distribution still differing by an unknown amount from that planned.

The iso-dose curves are altered due to the geometrical changes in treatment. The beams are incident upon a distorted surface, depth of penetration is different, relative tissue position, etc.
VI.2 Intra-modality ultrasound system

Image guidance in GUH is performed with an intra-modality 3D US system, Clarity\textsuperscript{TM}. To enable the intra-modality approach, the system is composed of two inter-connected US stations situated in the CT/US simulation room and in the treatment room respectively. Each station features a 2D US probe, fitted with an active infrared (IR) emitter array, and a ceiling-mounted infrared stereotactic camera. The probe’s absolute position during an US scan is tracked in real time by the camera, thus allowing the reconstruction of 3D US images of the target areas. The system is calibrated to the corresponding CT and Linac coordinate systems via a vendor supplied calibration phantom. The clinical work flow at GUH requires the initial acquisition of US images at CT/US simulation stage. These CT and US images are then fused and, according to GUH clinical practice, the prostate is manually segmented on the US image, thus defining the positioning reference volume (PRV). US scans are subsequently performed on a daily basis prior to treatment delivery in order to establish the location of the prostate with respect to the PRV. The location of the prostate immediately prior to treatment is compared to the location at the time of planning. Corrective couch shifts along the anterior-posterior AP, RL, and SI directions are then applied in order to realign the prostate to the correct nominal treatment position given by the PRV.

The key features of the Clarity\textsuperscript{TM} system can be summarised as follows.

- Daily 3D US images acquired in the treatment room are compared to the PRV acquired in the CT/US simulation room at the time of treatment planning.
- The absolute position of the US image planes are known using tracked infrared emitters fitted to the probe, thus permitting the reconstruction of 3D US images of the target areas.
The PRV was used to determine all daily displacements and was automatically superimposed on the daily images, and subsequently repositioned by the user until a best fit was obtained with the daily position. The difference between the PRV and the daily position determined prostate displacement. Using an US derived contour as the reference made this matching process easier to perform than using a CT derived contour. Intra-modality US has been reported to be more accurate than inter-modality US (Cury et al. 2006).

The Clarity\textsuperscript{TM} system in GUH has been proven to have a low inter-user variability, to have reproducible and temporally stable tolerances in all three directions of $\pm1$ mm and a cumulative tolerance of $\pm2$ mm for the phantom target localisation in the CT/US room and treatment room, respectively (Kleefeld et al. 2009). In comparison, the accuracy of a kV imaging system ExacTrac\textsuperscript{TM} (BrainLAB, Feldkirchen, Germany) that uses similar equipment to track motion has also been reported to be accurate within 2 mm (Fraser et al. 2010).
VI.3 Treatment planning and daily imaging in GUH

Patients diagnosed with prostate cancer in GUH are treated curatively with either CRT using a six-field coplanar beam technique or IMRT. Patients go through CT simulation imaging approximately 2 weeks prior to the start of treatment. Patients are in the supine position during simulation and treatment, knee supports are used and a Styrofoam pad is positioned between the ankles to ensure consistent leg positioning during planning and treatment. The prostate is defined as the GTV, as observed on 3 mm thick axial CT slices, with or without the proximal seminal vesicles depending on the risk of microscopic involvement, CTV. The PTV is comprised of a 7 mm margin in the posterior direction to spare the rectum, the PTV margin is 10 mm in all other directions around the CTV. The prescription dose is 74 Gy delivered to the PTV in 2 Gy fractions. During CT simulation and treatment, the patients are instructed to retain an empty rectum and a comfortably full bladder. The latter is confirmed by RT staff experienced with the Clarity\textsuperscript{TM} US system. Users are able to reproducibly achieve adequate image quality with minimal probe pressure as the prostate is scanned from an advanced superior position through the acoustic window of the bladder. Excessive probe pressure has been reported to displace the prostate by a maximum of 3 mm (Artignan et al. 2004) which is similar to the inter-observer variation in contouring the prostate on planning CT images (Rasch et al. 1999) and on daily megavoltage cone beam CT images (Bylund et al. 2008). For each fraction, the patient is first aligned to the room lasers based on tattoos. Next, an US image of the prostate is acquired. In this way, prostate displacement was determined as the difference in the position of the prostate, relative to tattoos, between the time of treatment planning and treatment delivery. Patients are then realigned based on the daily US localisation.
VI.4 Prostate displacement

The displacement statistics for the prostate are distilled into systematic and random displacement components and analysed using the following metrics (van Herk et al. 2000). The patient mean $\mu$, and the patient standard deviation $\sigma$, the group mean $M$, and the group standard deviation $\Sigma$, as well as the root mean square $\xi$ of all the patient standard deviations. The 3D displacement for daily prostate motion is also determined along with the average 3D displacement over all fractions. The systematic component describes a patient dependent constant displacement in the treatment preparation, that is, a constant shift between planning and treatment anatomy. The random component refers to the treatment execution, reflecting day to day variations about a systematic displacement. The systematic errors will cause a shift of the dose distribution with respect to the prostate, while the random errors will cause a blurring of the dose distribution.

- The systematic component $\Sigma$ is the standard deviation of all patient mean displacement values.
- The random component $\xi$ is the root mean square of all patient standard deviation displacement values.

PTV margins which ensure that 90% of the patients receive 95% of the prescribed dose can be estimated by use of the following equation (van Herk et al. 2000).

$$Margin_{PTV} = 2.5\Sigma + 0.7\xi$$  \hspace{1cm} (VI.1)

The potential use of the Clarity$^{TM}$ system to reduce treatment margins is examined by calculating margins based on the above metrics.
**FIGURE VI.3:** Impact of geometrical deviations on the dose distribution: The schematic shows the effect of geometrical deviations on the dose distribution defined in a coordinate system that is fixed relative to the prostate. (A) The random component deviations result in a blurred dose distribution. (B) The systematic component deviations result in a shift of the cumulative dose distribution relative to the prostate. Reproduced from (van Herk et al. 2000).

### VI.5 Inter-fraction organ motion in GUH

Prostate displacement statistics are provided by the *Clarity*\textsuperscript{TM} system which records clinical prostate displacements in GUH. Displacements are specified in the AP, RL, and SI direction. The data set is comprised of 56 patients who have successfully completed treatment with image guidance in GUH. Clinical RT treatment of the prostate in GUH is delivered in 37 fractions of 2 Gy per fraction, accumulating the prescribed dose of 74 Gy in the prostate. Fractions are delivered Monday to Friday with treatment suspended on Saturday and Sunday to aid the recovery of healthy tissue. US measurements of inter-fraction prostate motion for 56 patients at GUH is displayed in figure VI.7. The values in Table VI.2 are in agreement with other reported studies (van Herk et al. 1995; Roeske et al. 1995; Rudat et al. 1996; Melian et al. 1997; Tinger et al. 1998; Antolak et al. 1998; Stroom et al. 1999; Zelefsky et al. 1999; Fraser et al. 2010). Figures VI.4, VI.5, VI.6 display histograms of the individual fraction displacements for all patients, as well as patient systematic displacements compared to group systematic shifts.
The percentage of measurements that resulted in displacements greater than the calculated isotropic PTV margin of 15.5 mm based on equation VI.1, was 1.0%. These displacements were most frequent in the anterior-posterior plane than in any other, 0.7%, compared with 0.2% in the left-right plane and 0.1% in the inferior-superior plane. A searching algorithm applied to the displacement data revealed that a margin of 12.5 mm would achieve target coverage of approximately 95% of inter-fraction prostate organ motion in GUH. The algorithm sifts through the displacement data checking the absolute magnitude of the shifts in each plane, this is then compared to the size of the PTV margin in order to calculate if the displacement is outside of the PTV margin. The percentage of measurements that resulted in displacements greater than the PTV margin attained from the searching algorithm of 12.5 mm, was 4.3%. These displacements were most frequent in the anterior-posterior plane than in any other, 2.7%, compared with 0.9% in the inferior-superior plane and 0.7% in the left-right plane. The percentage of measurements that resulted in 3D major displacements, greater than the 10 mm PTV margin used clinically at GUH, was 14.7%. These major displacements were most frequent in the anterior-posterior plane than in any other, 8.7%, compared with 3.6% in the inferior-superior plane and 2.4% in the left-right plane. The percentage of measurements that resulted in displacements greater than the 5 mm reduced PTV margin, was 73.4%. These displacements were most frequent
FIGURE VI.4: Left - Right inter-fraction organ motion in GUH: The top graph displays mean patient displacements with patient standard deviations error bars. The solid horizontal line indicates the group systematic displacement M and the dashed horizontal lines indicate the systematic variation for each direction. The bottom graph is a histogram in each direction for all patient fraction displacements. The solid vertical line indicates the planned reference position and the dotted vertical lines indicate the 10 mm treatment margin. The histogram is Gaussian with constant variance, failing the Shapiro-Wilk test for Normality: $P = 0.0001$, $R^2 = 0.99$, W Statistic = 0.89, at a significance Level = 0.05.
Figure VI.5: Anterior - Posterior inter-fraction organ motion in GUH: The top graph displays mean patient displacements with patient standard deviations error bars. The solid horizontal line indicates the group systematic displacement $M$ and the dashed horizontal lines indicate the systematic variation for each direction. The bottom graph is a histogram in each direction for all patient fraction displacements. The solid vertical line indicates the planned reference position and the dotted vertical lines indicate the 10 mm treatment margin. The histogram is Gaussian with constant variance, failing the Shapiro-Wilk test for Normality: $P = 0.0003$, $R^2 = 0.96$, $W$ Statistic = 0.87, at a significance Level = 0.05.
**Figure VI.6:** Inferior - Superior inter-fraction organ motion in GUH: The top graph displays mean patient displacements with patient standard deviations error bars. The solid horizontal line indicates the group systematic displacement $M$ and the dashed horizontal lines indicate the systematic variation for each direction. The bottom graph is a histogram in each direction for all patient fraction displacements. The solid vertical line indicates the planned reference position and the dotted vertical lines indicate the 10 mm treatment margin. The histogram is Gaussian with constant variance, failing the Shapiro-Wilk test for Normality: $P = 0.0001$, $R^2 = 0.97$, $W$ Statistic $= 0.84$, at a significance Level $= 0.05$. 
in the anterior-posterior plane than in any other, 33.9%, compared with 21.6% in the inferior-superior plane and 17.9% in the left-right plane. This provides further support that margin reduction should only be considered in tandem with IGRT.

Based on the rigorous phantom based quality assurance procedures which guarantee the accuracy of the Clarity™ system, reproducing alignment tolerances of ±2 mm in the treatment room, PTV margins which ensure that 99% of the patients receive 99% of the prescribed dose can be estimated by using the following equation (van Herk et al. 2000).

\[
Margin_{PTV-IGRT} = 3.36\Sigma + 0.95\xi
\]  

Equation VI.2 calculates an isotropic PTV margin of approximately ±2.4 mm according to the ±2 mm accuracy of the Clarity™ system. From an inter-fraction organ motion management perspective, the use of PTV margins in excess
of more than triple this calculated value would seem to be grossly suboptimal use of the technology available. However, intra-fraction organ motion must now be considered. A study investigating the magnitude of intra-fraction prostate displacements during treatment reported that the prostate is displaced by 10, 7, 5 and 3 mm respectively, for 0.0%, 0.8%, 3.1% and 13.2% of the observation time, averaged over all fractions (Langen et al. 2008). It is on this basis that the use of IGRT with reduced margins, 5 mm PTV margins, is explored further in this work.

VI.6 Conformity number

The conformity number (CN) provides a quantitative evaluation of the degree of conformality of treatment plans.

\[
CN(d_{\text{ref}}) = \frac{V_{t_{d_{\text{ref}}}}}{V_t} \cdot \frac{V_{t_{d_{\text{ref}}}}}{V_{d_{\text{ref}}}}
\]

Figure VI.8: Parameters used for the calculation of the conformity number. \(V_t\) is the volume of the target. \(V_{t_{95}}\) and \(V_{t_{d_{\text{ref}}}}\) represent the volume and the target volume encompassed by the reference iso-dose \(d_{\text{ref}} = 95\%\) respectively.

The CN is calculated from the following equation (van’t Riet et al. 1997).
target volume. The second term refers to the volume of healthy tissues receiving a dose $d \geq d_{ref}$. CN increases with conformity ($0 \leq CN \leq 1$). The volumes involved in the definition of CN are shown in figure VI.8. It is important to note that $CN \approx 0$ when poor conformity is achieved ($V_{d_{ref}} \gg V_{t_{d_{ref}}}$) or when a geometrical miss occurs ($V_{t_{d_{ref}}} \approx 0$).

### VI.7 Deformation and modelling

The overall modelling and evaluation process can be decomposed into two constituent parts: structure deformation and radiobiological modelling.

**Figure VI.9:** The plan evaluation process: Initially the DICOM data set is read in by MatLab$^{TM}$, the RT structures of interest are imported into the workspace. The COP algorithm is applied to the imported RT structures, the newly deformed structures are formatted correctly according to the DICOM standard, a new DICOM data set is created with the newly deformed RT structures of interest, this new DICOM file is exported to either the TPS or MMCTP for dosimetric analysis, lastly the results of the analysis are then used as input parameters for the biological models, previously described.

Figure VI.9 gives an overview of the whole process from building and deforming RT structures using DICOM-RT datasets, to assessing the efficacy of treatment.
Improved quantification of IGRT treatment of the prostate

based on radiobiological metrics. It shows the modelling pipeline from acquisition of RT structures from DICOM-RT images to the construction and implementation of the deformation model. One of the main problems associated with the simulation of organ deformation is the conflicting demands of accuracy and computation time. In a clinical RT environment, both the accuracy of the deformation and the time required for computation are at odds with one another. Hence, a suitable model for organ deformation in RT treatment planning requires both computational efficiency and physical accuracy. Our model strives to enable the user to balance these two concerns against one another by allowing the user to control the level of accuracy and computation time. The COP algorithm for organ deformation is a novel approach and it is used to simulate the dynamic behaviour of organs undergoing displacement and deformation.

VI.8 Retrospective evaluation of four prostate patients

RT margins are designed to allow for organ motion and set up variation, however, the dose to the delineated structures is calculated assuming accurate delivery to static organs. Organ motion is a well documented moderator of treatment efficacy. In order to incorporate the effects of organ motion and deformation into treatment plan analysis, four prostate patients from GUH were randomly selected from the 56 patients who have successfully completed treatment with image guidance in GUH for retrospective evaluation. The dose distributions delivered to these structures and the resultant biological outcomes were calculated for each fraction, without the aid of image guidance, for the original CRT treatment plans and the deformed CRT treatment plans. Patient(1) exhibited the greatest dosimetric, and therefore biological, discrepancy between the deformed treatment plan and the original treatment plan. Patient(1) was replanned for UCRT treatment with the aid of image guidance. The realisation of margin reduction in RT so that the risk of complications in critical structures is diminished, ought to be paired with an escalation in the dose prescribed to the PTV, as the use of escalated doses in the radiation treatment of prostate cancer is linked with
a superior probability of cure. Patient(1) was replanned for an UCRT treatment with the aid of image guidance and with an escalated dose. Finally, MC dose calculation techniques, which use a first principles approach, are the most accurate dose calculation method. Previous work has shown a systematic non-negligible difference between MC methods and analytical algorithms in the pelvic region (Fraser et al. 2008). For this reasons, Patient(1) was also replanned using MMCTP which provides the ability to examine and assess the accuracy of TPSs compared to MC calculations using an unbiased independent common platform. Figure VI.10 depicts the inter-fraction prostate displacements simulated for the retrospective evaluation of four prostate patients previously treated at GUH.

The relative cumulative DVH data for the total delivered treatment was calculated by summing the absolute differential DVH data for each fractional 3D dose distribution delivered to the patient. This approach has the drawback that it does not discriminate between a systematic and a random displacement, however, the combined effect of these geometric discrepancies is captured in the DVH data and therefore subsequently in the dosimetric and biological modelling outcomes.
Figure VI.10: Individual inter-fraction prostate displacement of four patients at GUH: This data shows the clinically recorded inter-fraction prostate displacements of four patients previously treated at GUH. Image guidance in GUH is performed with the intra-modality 3D Clarity™ ultrasound system. The data set is comprised of 592 individual prostate shifts. Displacements are specified in the AP, RL, and SI directions along with a 3D resultant displacement. The mean AP, RL, SI and 3D displacements are -2.3 mm, -3.7 mm, -2.1, and 7.5 mm, respectively for patient(0). The mean AP, RL, SI and 3D displacements are 0.4 mm, -1.2 mm, -1.2, and 7.1 mm, respectively for patient(1). The mean AP, RL, SI and 3D displacements are -1.0 mm, -3.1 mm, -2.0, and 6.2 mm, respectively for patient(2). The mean AP, RL, SI and 3D displacements are -1.6 mm, -0.4 mm, 3.2, and 6.1 mm, respectively for patient(3).
VI.9 Results

Averaged over the group of patients, the change in TCP for the treatment in the unguided CRT scenario was -1.7%. If Patient(1), the patient with the greatest TCP discrepancy, 5.9%, is excluded, this value falls to -0.2%. This is in keeping with the conclusion that most patients treated with CRT are not compromised by inter-fraction organ motion. The considerable difference in TCP observed in Patient(1) is due to dose blurring caused by random prostate motion outside of the PTV margins, as recorded in fractions 20, 21, and 22 of patient(1)’s treatment.

With regard to the OARs, the NTCP of the rectum is more affected by motion than the NTCP of the bladder in the unguided CRT scenario. Averaged over the group of patients, the change in NTCP for the rectum in the unguided CRT scenario was 0.7%. The NTCP of the bladder was not altered by organ motion, 0%, this is due to the volume effect architecture of the rectum and bladder.

Table VI.3 displays the biological outcomes of the unguided CRT treatment of patient(1) based on the dose calculations of GUH TPS.

<table>
<thead>
<tr>
<th>TPS</th>
<th>Original (0.395)</th>
<th>Deformed (0.372)</th>
<th>Difference (0.023)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCP</td>
<td>65.8%</td>
<td>59.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td>NTCP rectum</td>
<td>8.2%</td>
<td>7.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>NTCP bladder</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP right femoral head</td>
<td>0.1%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NTCP left femoral head</td>
<td>0.0%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>UTCP</td>
<td>60.3%</td>
<td>55.1%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

The prostate is located in a uniform dose region, however the prostate was displaced outside of the PTV during fractions 20, 21, and 22. This resulted in a drop in the CN as well as a decrease in the TCP of patient(1). The bladder and rectum have a large dose gradient near or within their boundaries, making the dose to the bladder and rectum sensitive to motion. However, the relationship between dose and displacement depends on the shape and position of the organs.
Figure VI.11: CRT-DVH data for degradation of the dose delivered to the prostate patient(1) fraction 21: The DVH data reveals, in this instance, that the margins utilised in CRT are insufficient to ensure that unguided treatment will result in an acceptable dose curve for the GTV. The inter-fraction prostate motion experienced by patient(1) during fraction 21 produces a substantial cold spot within the prostate. The minimum dose delivered to the prostate during this fraction is approximately 1.4 Gy. The DVH data clearly illustrates this significant shortfall of the dose delivered to the prostate. The DVH data also shows that the dose distribution for the OARS is radically altered, with a substantial decrease in the rectal dose and a slight increase in the dose to the bladder. The net effect of this fraction is a considerable decline in the TCP of patient(1). The final NTCP of the rectum and bladder was virtually unaltered by this fraction due to random dose recovery in the OARs.

Figure VI.12: CRT-DVH data for the original and deformed RT structure sets patient(1): The DVH data shows that the dose distribution for the OARS is comparatively unchanged, with a slight reduction in the rectal dose. The DVH data also reveals, in this instance, that the margins utilised in CRT are insufficient to ensure that unguided treatment will result in an acceptable dose curve for the GTV. The unguided CRT treatment delivers a significantly lower dose to a proportion of the GTV than prescribed, this cold spot within the prostate results in a considerable reduction in TCP.
with respect to the iso-dose curves. For patient(1) the net result of the total inter-fraction organ motion was an almost unaltered DVH for the bladder and rectum.

Table VI.4 displays the biological outcomes of the planned UCRT and planned CRT treatment of patient(1) based on the dose calculations of GUH TPS.

**Table VI.4: Biological modelling outcomes for patient(1): Planned UCRT & Planned CRT**

<table>
<thead>
<tr>
<th>TPS</th>
<th>UCRT</th>
<th>CRT</th>
<th>Difference</th>
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</thead>
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<tr>
<td>CN</td>
<td>0.541</td>
<td>0.395</td>
<td>0.146</td>
</tr>
<tr>
<td>TCP</td>
<td>65.4%</td>
<td>65.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>NTCP rectum</td>
<td>4.5%</td>
<td>8.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>NTCP bladder</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP right femoral head</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>NTCP left femoral head</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>UTCP</td>
<td>62.5%</td>
<td>60.3%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

**Figure VI.13:** Planned UCRT & CRT DVH data for patient(1): The DVH data shows that the dose distribution of the UCRT plan is comparatively better to that of the CRT plan, with a significant reduction in the dose delivered to all of the OARs whilst also maintaining the prescriptive dose to the prostate.

Table VI.4 shows that TCP for both the planned UCRT and planned CRT treatment of patient(1) is approximately equivalent, with a difference of 0.4%. There is a remarkable decrease in the NTCP of the rectum, almost halving in value, a drop of 3.7%. The NTCP of the bladder remains unchanged. The NTCP of the right femoral head reduced by the minimum amount to 0%.
Figure VI.14: Iso-surface comparison of UCRT and CRT treatments: The iso-surfaces clearly demonstrate the difference in irradiated volume between UCRT treatment and CRT treatment. The large reduction in irradiated volume achieved through UCRT enables superior treatment to that of CRT, provided the target is definitely within the UCRT treatment volume. The prostate contours are shown in blue and 95% of the prescription dose is overlaid in translucent red.
Improved quantification of IGRT treatment of the prostate

Despite the NTCP of the rectum being reduced by approximately a factor of two attributable to UCRT treatment, the net gain in UCTP is minor, a modest increase of 2.4%.

Table VI.5 shows that the TCP for the planned UCRT treatment of patient(1) is deliverable through imaged guided UCRT treatment, with a difference of 0.2% between the planned treatment and the delivered treatment. There is a 1.4% increase in the NTCP of the rectum, this is attributable to the predominately posterior organ motion of patient(1). The NTCP of the bladder and femoral heads remains unchanged at 0%.

<table>
<thead>
<tr>
<th>TPS</th>
<th>Original</th>
<th>Deformed</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>(0.541)</td>
<td>(0.482)</td>
<td>(0.059)</td>
</tr>
<tr>
<td>TCP</td>
<td>65.6%</td>
<td>65.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>NTCP rectum</td>
<td>4.5%</td>
<td>5.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>NTCP bladder</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP right femoral head</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP left femoral head</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>UCTP</td>
<td>62.3%</td>
<td>61.5%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Figure VI.15: Planned UCRT & delivered UCRT DVH data for patient(1): The DVH data shows that the dose distribution of the planned UCRT treatment is comparatively better to that of the delivered UCRT treatment. The DVH data shows that the guided treatment delivers an acceptable dose curve for the prostate, however, due to the prevalent posterior organ motion of patient(1), the dose to the rectum increased and the dose to the bladder decreased, resulting in a net decrease in UCTP of approximately 1%.
Table VI.6 shows the remarkable improvement attainable in TCP for the planned optimised UCRT treatment of patient(1) compared with conventional CRT. A substantial increase of over 17% is observed in TCP for the optimised UCRT treatment, this is achieved through dose escalation and image guidance. The prescription dose delivered to Patient (1) was escalated to the limit of the dose constraints used in GUH, the limiting dose constraint for patient(1) was the 4th rectal dose constraint. This corresponded to a prescription dose of 80 Gy in 40 fractions. With regard to the OARs, a difference of 1.7% in the NTCP of the rectum was observed between the conventional CRT treatment and the optimised UCRT treatment. There was no significant difference observed in the other OARs.

Table VI.6: Biological modelling outcomes for patient(1): Conventional CRT & dose escalated UCRT

<table>
<thead>
<tr>
<th>TPS</th>
<th>C-CRT (0.395)</th>
<th>DE-UCRT (0.541)</th>
<th>Difference (0.146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCP</td>
<td>65.8%</td>
<td>83.2%</td>
<td>17.4%</td>
</tr>
<tr>
<td>NTCP rectum</td>
<td>8.2%</td>
<td>9.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>NTCP bladder</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP right femoral head</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>NTCP left femoral head</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>UTCP</td>
<td>60.4%</td>
<td>74.8%</td>
<td>14.4%</td>
</tr>
</tbody>
</table>

The difference in UTCP for the planned optimised UCRT treatment of patient(1) compared with conventional CRT is approximately 14%. This represents a considerable improvement in the therapeutic ratio of patient(1).

Table VI.7: Biological modelling outcomes for patient(1): Guided conventional UCRT

<table>
<thead>
<tr>
<th>UCRT CN</th>
<th>TPS (0.541)</th>
<th>MMCTP (0.541)</th>
<th>Difference (0.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCP</td>
<td>65.4%</td>
<td>66.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>NTCP rectum</td>
<td>4.5%</td>
<td>3.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>NTCP bladder</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NTCP right femoral head</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>NTCP left femoral head</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>UTCP</td>
<td>62.5%</td>
<td>64.9%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>
Figure VI.16: Optimised UCRT & conventional UCRT DVH data for patient(1): The DVH data shows the large gain in the dose distribution deliverable to the prostate through optimised UCRT. The DVH data shows that the Optimised UCRT treatment plan delivers a superior dose curve for the prostate whilst producing acceptable dose curves for the rectum and bladder. The DVH data shows the sparing in the volume of the OARs irradiated through optimised UCRT. However, due to the escalation in the prescription dose of patient(1), the dose to the rectum and bladder is increased, resulting in a net increase in NTCP of approximately 2% and 0% respectively. Despite this, the optimised UCRT treatment plan results in a net increase of approximately 14%.

These discrepancies can be attributed to differences in dose calculation algorithms between the TPS and MMCTP. This however does serve as a proof of concept for the implementation of MMCTP.

Figure VI.17: MMCTP DVH data for conventional UCRT of patient(1): The DVH data shows a considerable change in the the dose delivered to all of the OARS and the prostate when compared with the TPS. The patient geometry and electron density distribution in this MMCTP recalculation was based on the initial CT dataset. For comparison with the TPS appropriate stopping power ratios were applied to compute the dose-to-water from the dose-to-medium.
Figure VI.18: MC-TPS axial dose comparison: The dose distributions from the 6 field ultra conformal prostate plan, axial view, from the MC simulations (top) and the TPS (bottom). The comparison reveals discrepancies between the two dose distributions: The MC dose distribution predicts a different dose in the femoral heads and rectum as well as a higher dose in the prostate, when compared with the TPS dose distribution.

VI.10 Discussion on the improvement IGRT

The results show that in the majority of cases conventional CRT with current PTV margins is sufficient to ensure that unguided treatment results in an adequate therapeutic ratio for the patient. However for some patients, inter-fraction organ motion is considerable and significantly moderates the clinical outcome. For these patients image guidance is employed to deal with this challenge. This
 Improved quantification of IGRT treatment of the prostate

Figure VI.19: MC-TPS sagittal & coronal dose comparison: The dose distributions from the 6 field ultra conformal prostate plan, sagittal & coronal views, from the MC simulations (top) and the TPS (bottom). The comparison reveals discrepancies between the two dose distributions: The MC dose distribution predicts a different dose in the rectum and femoral heads as well as a higher dose in the prostate, when compared with the TPS dose distribution.

is an effective method of ensuring that the planned dose to the target is actually delivered to the patient. Nevertheless, the potential for further improvement is always existent.

The emphasis in this present work was to explore the effects of margin reduction with IGRT treatment. The presence of inter-fraction prostate motion was accounted for using in house deformation software based on clinical measurements using the intra-modality 3D US system, Clarity\textsuperscript{TM}. Prostate displacement statistics were analysed. Displacements were specified in the AP, RL, and SI directions. An isotropic PTV margin of approximately $\pm 2.4$ mm according to the $\pm 2$ mm accuracy of the Clarity\textsuperscript{TM} system was calculated. The use of PTV margins in
Improved quantification of IGRT treatment of the prostate

excess of more than triple this calculated value would seem to be grossly subop-
timal use of the technology available. However, intra-fraction organ motion must
be allowed for. Intra-fraction prostate displacement during treatment has been
reported to be 0.0%, 0.8%, 3.1% and 13.2% of the observation time averaged
over all fractions for 10, 7, 5 and 3 mm displacements respectively (Langen et al.
2008). It is on this basis that the use of IGRT with 5 mm PTV margins was
explored further in this work.

Four patients were randomly selected from the 56 patients who have success-
fully completed treatment with image guidance in GUH. These Patients were
replanned using the TPS to assess the biological outcomes associated with their
inter-fraction organ motion.

The results show that, with respect to unguided CRT, there was virtually no
alteration in the UTCP of three of the four patients. However, Patient(1) ex-
perienced a significant deterioration in TCP and therefore did benefit from and
require the IGRT utilised during the course of their treatment at GUH.

The goal of evaluating prospective improvements in RT treatment was exam-
ined further by replanning patient(1) with reduced PTV margins. This approach
showed that at the planning stage, patient(1) benefited from a relative increase
of 37% in conformality. The results also showed a minor improvement of 2.4%
in the therapeutic ratio is inherently attainable with UCRT using a conventional
prescription dose and fractionation regime. This is despite the advantage of a re-
duction in rectal NTCP by almost a factor of two. So with regard to the rectum
a large relative benefit was obtained through UCRT treatment. Additionally, the
desired TCP was shown to be deliverable with the aid of image guidance. A large
relative change in the NTCP of the rectum was predicted, a difference of 1.7%
between the planned and delivered treatments. This difference in the NTCP of
the rectum is due to the unique displacement statistics of patient(1). Patient(1)
Improved quantification of IGRT treatment of the prostate

experienced predominately posterior prostate motion, and as a consequence the proportion of the rectal volume within the treatment field was generally larger during a treatment fraction than planned. This discrepancy in NTCP could be, in principle, reduced by continuous replanning of the patient after each fraction of treatment. This would however place large pressure on the work load of a RT department and the merits of this are debatable from a time management and resources perspective.

These results lead us to examine the potential role of dose escalated UCRT with image guidance, in the context of patient(1).

The conventional CRT plan TCP of 65.8% dramatically increases to 83.2% for the dose escalated UCRT plan, this is an increase of approximately 17% in the TCP for patient(1). The NTCP of the OARs holds reasonably constant for patient(1), a change of 1.7% in the rectum. The conventional CRT plan UTCP of 60.4% rises by 14.4% to 74.8% for the dose escalated UCRT plan.

The optimisation of UCRT with image guidance through dose escalation in the 2 Gy per fraction regime is reassuring from a clinical position, as all of the dose constraints employed in GUH are based on clinical experience in this fractionation regime. Therefore dose escalation up to the limits imposed by the radiation oncologists of GUH, can be viewed with a certain degree of confidence.

The absolute values of the immediate findings in this simulation are distinct to patient(1), and other patients would naturally give different results. However, this does not weaken the relative values used to evaluate if UCRT treatment is superior to CRT. From a radiobiological and displacements perspective, Patient(1) was inherently suboptimal. Patient(1) had a very large prostate (the Mean + 3SD, see Figure IV.5) and relatively small rectum, this combination results in a poor TCP, NTCP and therefore UTCP biological outcome. Furthermore, the
inter-fraction prostate motion of Patient(1) was mainly posterior in direction, in general this leads to a greater proportion of the rectal volume falling within the treatment field during a treatment fraction than planned. This again leads to a poor NTCP and therefore UTCP biological outcome. The volume effect is witnessed here in relation to TCP, the very large tumour volume leads to a less than average outcome for the TCP value. The volume effect is witnessed here in relation to the NTCP of the bladder, the large bladder volume resulted in no predicted toxicity associated with the bladder. The inverse was witnessed for the volume effect with regard to NTCP, the relatively smaller rectum volume corresponded with a relatively large NTCP value. These biological outcomes due to the volume effect are in accord with previous reported biological outcomes studies (Bentzen and Thames 1996; Bentzen et al. 2010; Michalski et al. 2010; Viswanathan et al. 2010; Marks et al. 2010). The accuracy of the TCP model has been clearly quantified in this work, see Chapter II. Conversely, extra caution should be applied in the use of the LKB NTCP model, even though the LKB NTCP model is generally acknowledged as the most suitable NTCP model for the analysis and evaluation of external beam RT plans in the case of the rectum and bladder. The LKB NTCP most likely overestimates the complication rate witnessed in the rectum. The LKB NTCP model in this study predicts a planned risk of 8.2% for rectal injury from a total delivered dose of 74 Gy, however, a clinical study conducted by (Rancati et al. 2004) reported NTCP rectal injury rates of 1.6% from a cohort of 547 patients treated up to a total dose of 79.2 Gy.

Finally for patient(1), a small improvement was predicted between conventional UCRT and conventional CRT, a significant improvement was predicted between dose escalated UCRT and conventional CRT. These findings require confirmation.
VI.11 Conclusions of IGRT simulation

The current work demonstrates the radiobiological effect of conventional CRT, conventional UCRT and dose escalated UCRT.

Treatment delivery through CRT and UCRT in the instance of both guided and unguided treatment were simulated and analysed. Geometric uncertainties pertaining to clinically observed inter-fraction prostate motion, via the Clarity\textsuperscript{TM} system, were incorporated into the simulation and modelling process through the use of in house organ deformation software. The radiobiological effect of the different treatment types were evaluated using diverse biological factors. The results show that the UCRT for the delivery of RT treatment is, as expected logically, superior to CRT treatment. The use of UCRT is advocated only on the provision that IGRT is available to ensure that treatment delivery per fraction delivers the planned target coverage to the CTV. The results clearly show that in order to fully optimise the benefits offered through UCRT, dose escalation in conjunction with image guidance is necessary.

A number of the initial conclusions which can be drawn from the study include:

1. There is no discernible difference between guided and unguided conventional CRT for the majority of patients.

2. In order to deliver UCRT, image guidance per fraction is required.

3. In order to fully optimise UCRT, dose escalation is required.

These findings advocate that UCRT should be considered for clinical implementation in RT centres where existing image guidance capabilities are available. The results show that dose escalation, to local OAR dose volume constraints, should also be considered due to the large gains attainable in the therapeutic ratio. These
findings culminate to a final recommendation that a phased introduction of dose escalated UCRT with image guidance, along with continuous clinical review, be considered for clinical implementation in the RT department of GUH.
Final conclusions, contribution to knowledge and future work

VII.1 Final conclusions

A principal focus of this study was to develop a mechanistic TCP model, using radiobiologically sound input parameters, to accurately predict treatment outcomes for a wide range of treatment strategies. The TCP model presented in this thesis for external beam treatment of intermediate risk prostate cancer has been demonstrated to accurately forecast the 5 year bNED clinical outcomes of hypo-fractionation, standard-fractionation, and hyper-fractionation RT using optimised radiosensitivity parameters produced by the NM simplex algorithm. A statistical analysis of the TCP models’ predictions, measured against the hyper, standard, and hypo-fractionated treatment 5 year bNED clinical outcome data, resulted in an $R^2$ value of 0.92 and a RMSE of 1.39%. In addition, this TCP
model using the optimised radiosensitivity values listed in Table II.3 has been demonstrated to be likely to correctly predict the 5 year bNED clinical outcomes of SBRT. The average value for $\alpha$ and the average value for $\alpha/\beta$ are similar to parameters obtained in previous meta-analysis studies, both these values were obtained by the NM simplex algorithms’ search of the radiosensitivity solution space of the 5 year bNED clinical outcome data set for hyper, standard, and hypo-fractionated RT treatments. These values were obtained through a robust fitting procedure using the NM simplex algorithm based upon the best available clinical data for dose response, total initial clonogen number, clonogen density, clonogen distribution, and hypoxia status of the average intermediate risk prostate cancer patient. This TCP model has radiobiological merit by harmonising current theoretical knowledge with current experimental data. These results lead us to conclude that this TCP model, used with the optimised radiosensitivity values obtained by the NM simplex algorithms’ search of the radiosensitivity solution space of the 5 year bNED clinical outcome data set for hyper, standard, and hypo-fractionated RT treatments, is appropriate for the analysis and evaluation of external beam RT plans with regard to tumour control for a wide variety of RT treatment scenarios under these clinical conditions.

Another key feature of this thesis was to create in-house organ deformation software to account for inter-fraction organ motion. The deformation code replicates realistic anatomical deformation through compression and expansion of the OARs based upon the displacements of the prostate. The deformation code is based upon structures of vertices built in a virtual DICOM environment. The deformation code was developed to allow inter-fraction organ motion to be incorporated easily into RT treatment plans. The deformation code offers the ability to dynamically account for inter-fraction organ motion in treatment planning, facilitating a fraction by fraction evolutionary approach to treatment planning. This software was successfully applied to clinical DICOM-RT files of four prostate cancer patients at GUH.
A further aim of this work was to ascertain a MC linac model that agreed to measured data to within 3% so that it could be used as a verification tool for non-standard clinical treatment plans. An efficient tuning method has been implemented using the BEAMnrc and DOSXYZ MC codes. For the 15 MeV Siemens Oncor linac, the MC dose profile simulations along with the RMSD analysis of the measured data indicated that an energy of 13.5 MeV for the incident electron beam together with a radial distribution of 0.15 cm for the beam radius produced the best fit with the least variance to the measured data. These parameters produce a MC value, on average after $D_{\text{max}}$ and within the flat field of the beam, within ±1.0% of the measured data for the PDDs and TDPs curves simulated for the different field sizes ($20 \times 20 \text{ cm}^2$, $10 \times 10 \text{ cm}^2$, $5 \times 5 \text{ cm}^2$). For this Siemens Oncor 15 MeV model, the PDDs all agree within ±0.9% after $D_{\text{max}}$. The Siemens model TDPs agree within ±0.4% inside of the penumbra with an accuracy of ±3 mm. A dose calculation method using MC techniques has also been used and developed for the verification of patient treatments. Good agreement has been shown between MC and conventional TPS for a single patient. An accurate model has been developed for the Siemens Oncor linear accelerator that allows the modelling of a wide variety of treatment fields. The MC model of the Siemens linac made use of BEAMnrc/DOSXYZnrc and MMCTP. This model opens the possibility of large scale retrospective and prospective MC studies in GUH.

Based upon these realisations optimal PTV margins were calculated for 56 prostate patients using statistical analysis of inter-fraction organ motion, recorded at GUH using an intra-modality 3D US system, Clarity$^{\text{TM}}$. The predicted biological effect of these margin sizes was explored in both a phantom study and clinical prostate cases. The results showed for intermediate risk prostate patients, substantial improvements in therapeutic ratios can be delivered through image guidance, margin reduction and dose escalation. This outcome is achieved simply by optimising the technology and protocols currently available and in use in the RT center at GUH. The final conclusion of this thesis is that intermediate risk prostate cancer
patients can obtain substantial improvements in their therapeutic ratio through the use of image guidance, margin reduction and dose escalation.

VII.2 Contribution to knowledge

There are several defined ways in which a Ph.D. can be original and therefore contribute to knowledge (Phillips 1992; Phillips and Pugh 2000). This research has met the following defined ways:

- Carrying out empirical work that has not been done before – a meta-analysis of clinical outcomes for a wide range of RT treatments, hyper-, standard, and hypo-fractionated treatments was performed, an analysis not previously reported on.

- Making a synthesis that has not been made before – this research addresses TCP modelling in intermediate risk prostate cancer. The fitting process produced biologically plausible radiosensitivity parameters for the bi-variate Gaussian distributed Poisson TCP model, overcoming a key flaw in previous TCP modeling studies.

- Bringing new evidence to bear on an old issue – the TCP model fit was based upon the best available clinical data for dose response, total initial clonogen number, clonogen density, clonogen distribution, and hypoxia status of the average intermediate risk prostate cancer patient.

- Being cross-disciplinary and using different methodologies – a central element of this thesis was the successful combination of biological modelling, radiation transport modelling and organ deformation modelling, all fundamental to RT treatment.

- Looking at areas that people in the discipline have not looked at before – the prospective ability of the TCP model to predict clinical outcomes for SBRT was quantitatively evaluated, an analysis not previously conducted.
• Adding to knowledge in a way that has not been done before – a comprehensive quantitative system, utilising biological modelling, radiation transport modelling and organ deformation modelling, for the analysis and ranking of external beam RT plans, for intermediate risk prostate cancer patients, has been developed. Such a comprehensive quantitative system has not been previously reported.

VII.3 Future work

Future work is planned for the evaluation of the remaining 52 intermediate risk prostate patients who successfully completed treatment with image guidance in GUH.

Future work would also include a comprehensive validation of the deformed geometry produced by the deformation code, this would be done though the use of multiple/repeat CT data sets.

Other future work includes the application of the techniques and methods used in this work for the case of the prostate, to the case of the lung. This would require fitting a new TCP model and new NTCP model to the clinical data available in the literature for the lung. The organ deformation code would be adapted for the lung and also parallelised in order to bring the computation time down from minutes to seconds. The heterogeneous structures of the thorax are ideally suited for MC simulations.


Bibliography


Bibliography


Bibliography


