EXPERIMENTAL VALIDATION OF MATHEMATICAL MODELS TO INCLUDE BIOMECHANICS INTO DOSE ACCUMULATION CALCULATION IN RADIOTHERAPY

by

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A thesis submitted in conformity with the requirements for the degree of Master of Health Science
Graduate Department of Institute of Biomaterials and Biomedical Engineering
University of Toronto

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ABSTRACT

Inaccurate dose calculation in radiotherapy can lead to errors in treatment delivery and evaluation of treatment efficacy. Respiration can cause of intra-fractional motions, leading to uncertainties in tumor targeting. These motions should therefore be included in dose calculation. The finite element method-based deformable registration platform MORFEUS is able to accurately quantify organ deformations. The dose accumulation algorithm included in MORFEUS takes organ deformation and tumor movement into account. This study has experimentally validated this dose accumulation algorithm by combining 3D gel dosimetry, respiratory motion-mimicking actuation mechanism, and finite element analysis. Results have shown that within the intrinsic measurement uncertainties of gel dosimetry, under normal conformal dose distribution conditions, more than 90% of the voxels in MORFEUS generated dose grids have met the criterion analogous to the gamma test. The average (SD) distance between selected pairs of isodose surfaces on the gel and MORFEUS dose distributions is 0.12 (0.08) cm.
To my family, friends, supervisors, and colleagues

To everyone who is there for me through this work and in every aspect of life
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<td>Four-Dimensional Cone-Beam Computed Tomography</td>
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<td>4D CT</td>
<td>Four-Dimensional Computed Tomography</td>
</tr>
<tr>
<td>ABC</td>
<td>Active Breathing Control</td>
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<td>AP</td>
<td>Anterior-Posterior</td>
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<tr>
<td>CBCT</td>
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<tr>
<td>CCD</td>
<td>Charge-Coupled Device</td>
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<tr>
<td>COM</td>
<td>Centre of Mass</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>Finite Element Analysis</td>
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<td>FEM</td>
<td>Finite Element Model</td>
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<td>FOV</td>
<td>Field of View</td>
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<td>GTV</td>
<td>Gross Tumor Volume</td>
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<td>High-Density Polyethylene</td>
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<td>Polyvinyl Alcohol</td>
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<td>Quality Assurance</td>
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<tr>
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<td>Description</td>
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<td>RILD</td>
<td>Radiation Induced Liver Disease</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-Inferior</td>
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<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
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<td>Echo Time</td>
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<tr>
<td>THP</td>
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CHAPTER 1 : Introduction
1. Liver Cancer and Treatment Options

Cancer accounts for 13% of total death worldwide in 2007. The number of cancer deaths is expected to increase globally by 45% from 2007 to 2030 due to population aging and unhealthy life style. Liver cancer is the third deadliest type of cancer after lung and stomach cancers\(^1\). Liver cancers can be both primary and secondary. The 5-year survival rate for primary liver cancer is 32.5%, but early stage patients have a higher 5-year survival rate of 59.1%\(^58\). Secondary liver cancer is about 20 times more common than primary liver cancer in US. The rich vasculature and the blood processing function of liver make it the second most common secondary cancer site\(^59\). Commonly used treatments and disease management options for liver cancer are surgery, chemotherapy, and radiotherapy. Different options can be combined to achieve optimal treatment outcome\(^2\).

1.1 Surgery

Surgery is performed before evidence of metastasis is displayed, and it is likely that the entire tumor can be surgically removed\(^2\). Surgery has the highest prognosis for liver cancer patients with tumors less than 5 cm in diameter. However, many patients are diagnosed with a larger tumor or multiple tumors and have other conditions such as cirrhosis or hepatitis, making them ineligible for surgery. In fact, less than 15% of liver cancer patients are eligible for surgical resection\(^59, 60\).

1.2 Chemotherapy

Chemotherapy refers to using medication to treat cancers. Chemotherapy drugs generally attack actively dividing cells during chromosome duplication or mitosis. The medications
can be taken by oral administration, intramuscular or subcutaneous injection, and intravenous perfusion. Unlike surgery, which is an option for local tumor treatment, chemotherapy is regarded as a more systemic treatment since drugs distribute throughout the body and destroy cancer cells wherever they have spread to. Due to their mechanism of action, chemotherapy medications also attack healthy cells that undergo normal reproduction for tissue replacement and repair, and therefore can cause side effects. Sites that are particularly vulnerable to chemotherapy side effects include skin, hair follicles, reproductive organs, and bone marrows. When treating liver cancer patients, chemotherapy can be used in conjunction with embolization, which refers to blocking one of the liver’s arterial blood supplies to starve the tumor, but also damaging normal liver tissue.

1.3 Radiotherapy

In radiation therapy, also called radiotherapy (RT), ionizing radiation is delivered to damage the DNA molecules in cell nuclei, and subsequently cause cell death at the next division phase. Radiotherapy can be classified into curative, adjuvant, and palliative treatments, depending on the treatment intent. Curative RT aims at eliminating the tumor, and high dose that requires high-precision localization is often used. Adjuvant RT supports surgery and uses lower doses than curative RT. The purpose of palliative RT is not to cure the cancer, but to relieve cancer-related symptoms and complications. The scale, complexity, and dose level of palliative RT vary depending on the disease condition and treatment goal.

Radiation energy can be carried by photons, including X-ray and gamma ray, or particles such as electrons, protons, and neutrons. Photons are the most commonly used radiation type in radiotherapy. Photons are either emitted from sealed or unsealed radioactive sources, such
as cobalt, or generated from linear accelerators, which accelerate electrons to high velocities and let them collide into a metallic X-ray target, generating photon beams by the mechanism of Bremsstrahlung production. The penetration depth of a beam is proportional to its energy. If the X-ray target is removed, linear accelerators would emit electrons, which do not penetrate into the body as deeply as photons do. Electrons are generally used in superficial treatments\textsuperscript{5}. Protons and neutrons are less frequently used in radiotherapy. Treatments delivered by linear accelerators are referred to as external beam radiotherapy (EBRT) because the source of radiation is outside the patient’s body.

Similar to chemotherapy medications, radiation kills actively reproducing cells, which include both cancerous cells and normal cells. This has imposed a great challenge in using EBRT to treat liver cancers, because normal liver tissue has a low tolerance to ionizing radiation. It has been shown that a dose of 120 Gy is required to kill a primary liver tumor, while the surrounding normal hepatic tissue can tolerate only 30 to 35 Gy. Dose beyond this limit might cause radiation-induced liver disease (RILD), which includes venal occlusion in the liver and hepatocyte atrophy\textsuperscript{62}. Accurate and precise targeting is therefore required to deliver high dose to the tumor while sparing the surrounding healthy tissues as much as possible.

2. Radiotherapy Treatment Planning

2.1 Treatment Planning Simulation

Before planning an RT treatment, an image of a patient’s internal anatomy is first acquired using medical imaging modalities such as fluoroscopy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). This imaging
process is referred to as simulation, since the acquired image is a representation of the patient’s anatomy on which treatment plans can be designed, simulated, and modified. CT is the most commonly used simulator, because CT images accurately reflect the geometries of the patient’s anatomy and provide the Hounsfield number for each type of tissue, which indicates the stopping power of a tissue to ionizing radiation, and is an essential piece of information in dose calculation. Sometimes other imaging modalities such as MRI are also used to provide better soft tissue contrasts to enable a more clear visualization of the tumor. Since geometrical distortions can occur in MR images, they are always correlated to the CT images through the process of image registration.

Simulations can be 2D, 3D (CT, MRI), or 4D (respiration correlated CT or 4D CT), depending on treatment intent and the size, shape, and location of the tumor. For simple and whole body palliative treatments, since low dose is often prescribed and precise volumetric targeting is not important, 2D simulation is often sufficient. Some palliative treatments can be highly complicated if the location of the legion is close to a critical structure such as the spinal cord. In these cases, precisely localized radiation delivery is required, thus 3D simulation becomes necessary.

2.2 Delineation on Treatment Planning Images

The nearby healthy structures that are sensitive to radiation are referred to as organ at risk (OAR). The physiological functions of a structure can be serial or parallel. Serial function such as neural signal conduction, are permanently deteriorated if the corresponding anatomy, such as the spinal cord, is damaged. For serial structures, the maximum dose to the OAR must be minimized when planning the treatment. Parallel functions can be restored or
compensated when some tissue damage occurs. For example, the liver still preserves hepatic functions even when part of it is surgically removed. For parallel structures, the mean dose to a given volume of healthy tissue is typically minimized. 4D CT is sometimes used in lung cancer treatment planning to quantify respiration induced tumor motion. The treatment can then be properly designed to ensure that the tumor is always under beam coverage through breathing cycles.

Once the simulation images are obtained, the radiation oncologist evaluates them and contours a gross tumor volume (GTV), which is the visible tumor mass on the images, and a clinical target volume (CTV), which adds a margin around the GTV to include the filtration of cancerous cells into the surrounding tissues that is not visible on images. Then a radiation therapist develops a planning target volume (PTV), which further expands the CTV to account for possible geometric localization errors and changes in tumor position and OAR position\(^7\) (See Figure 1.1).
**2.3 Prescription and Dose Calculation**

Radiation dose is prescribed to the regions of interest (ROI). The dose distribution is often designed so that 95% of PTV is covered with at least 95% of the prescribed dose, while OAR should only receive a dose below their tolerance\(^7\). Technological advances have enabled the region of high dose coverage to conform tightly (on the scale of millimetres) to tumors with irregular shapes by targeting the tumor from different directions, and changing the intensity and/or shape of the radiation beams. Conformal radiation therapy, particularly intensity modulated radiation therapy (IMRT), utilizes this technique to optimize beam arrangement and radiation delivery\(^8\) (See Figure 1.2).
Figure 1.2. The simulated beam arrangement and resulted dose distribution of a conformal RT plan on the CT image of the same liver cancer patient in Figure 1.1.

High dose is delivered to the PTV avoiding as much of the normal liver tissue as possible.

RT treatment is typically fractionated, meaning that the prescribed dose is delivered over a number of treatment sessions called fractions. The purpose is to allow healthy tissues to recover from radiation damage between fractions. The entire course of treatment typically lasts 2 to 8 weeks and consists of more than 5 fractions. Standard fractionation protocols deliver a dose of 2 Gy in each treatment fraction. However, recent studies have discovered the potential benefits of hypo-fractionated RT, composed of less than 5 fractions with a dose of 10 to 30 Gy or more delivered in each. The advantages include fewer trips to the hospital, shorter overall course of treatment, possible improvement in tumor control, and potential
reduction in toxicity\textsuperscript{9,10}.

2.4 Treatment Verification Parameters

Once a treatment plan has completed, it is important to verify that the delivered dose matches with the prescribed dose, especially in cases of IMRT. Treatment verification is usually done by comparing the dose distribution measured with dosimetric devices with the planned distribution. A number of parameters have been developed to describe the result of such comparisons. Some commonly used parameters include dose difference, distance-to-agreement (DTA), and gamma (\(\gamma\)) index\textsuperscript{51,53,56,57}.

As its name suggests, dose difference simply refers to the point-by-point difference in dose levels between two dose distributions. A drawback of using dose difference is that it is overly sensitive in regions with steep dose gradients. Small spatial offset between the two dose grids being compared would yield large dose differences in those regions. Therefore, dose difference is most suitable in regions with low dose gradients.

Distance-to-agreement (DTA) addresses the over-sensitivity of the dose difference parameter in steep dose gradient regions. For one point in the planned dose distribution, the nearest point with the same dose value is found in the measured dose distribution, and the distance between the two points is defined as the DTA. In steep dose gradient regions, small positional offset between the two dose distributions does not skew DTA to overly large values. However, in contrast to dose difference, DTA is overly sensitive in regions with low dose gradients, where small dose differences may lead to a large DTA\textsuperscript{56,57}.

To utilize the strengths of dose difference and DTA while avoiding their respective
limitations, the gamma(\(\gamma\)) index was developed by Low et al as a composite of the two parameters. Gamma index is independently calculated at each voxel in the planned distribution using the entire measured dose distribution. The mathematical formula to calculate \(\gamma\) are as follows:

\[
\Gamma(\vec{r}_m, \vec{r}_p) = \sqrt{\frac{r^2(\vec{r}_m, \vec{r}_p)}{\Delta d^2} + \frac{\delta^2(\vec{r}_m, \vec{r}_p)}{\Delta D^2}}
\]

EQN 1.1

\[
\gamma(\vec{r}_p) = \min\{\Gamma(\vec{r}_m, \vec{r}_p)\} \forall \{\vec{r}_m\}
\]

The general \(\Gamma\) function described in the first equation is calculated for all points \(\vec{r}_m\) on the measured dose distribution and all points \(\vec{r}_p\) on the planned distribution. \(r(\vec{r}_m, \vec{r}_p)\) is the spatial distance between a point \(\vec{r}_m\) on the measured dose distribution and a point \(\vec{r}_p\) on the planned distribution. \(\delta(\vec{r}_m, \vec{r}_p)\) is the dose difference between \(\vec{r}_m\) and \(\vec{r}_p\). \(\Delta d\) is the predetermined DTA criterion, which is commonly 2 mm or 3 mm; and \(\Delta D\) is the predetermined dose difference criterion, which is commonly set to be 2\% to 5\%. The second equation defines \(\gamma\) for each point \(\vec{r}_p\) on the planned dose distribution to be the minimum \(\Gamma\) for all points in the measured dose distribution\(^{51}\).

3. The Issue of Patient Anatomy Displacement in RT

Since treatment plans usually remain unchanged throughout the course of treatment, it is important to ensure that the tumor and OARs are at the same location in each fraction as they have been during treatment planning. Unfortunately the position and geometry of both
the tumor and the OARs would inevitably change between the time of planning and the time of treatment delivery, between fractions (i.e. inter-fractional displacement), and during a fraction (i.e. intra-fractional displacement). These variations can cause errors and uncertainties in radiation delivery. The errors are particularly of concern when steep spatial dose gradients outside the PTV are planned to reduce the dose delivered to a nearby critical OAR. In this case, the OAR can be pushed inside the high dose region by small displacements. Also comparing with conventional treatment schedules, localization errors in hypo-fractionated treatments would cause a higher dose to be delivered to the surrounding healthy tissue\(^{11}\). Therefore considerable efforts have been dedicated to developing accurate tumor targeting techniques to accommodate for inter-fractional and intra-fractional displacements\(^{12,13}\).

### 3.1 Inter-fractional Variations

Inter-fractional variations in patient anatomy and tumor position can be addressed by patient setup and image guidance techniques. Patient setup involves establishing a common coordinate system that is used in both treatment planning and delivery. The coordinate system is defined by the radiation isocentre, which is the converging point of radiation beams delivered from different directions. The isocentre is identified by three intersecting orthogonal laser beams in the treatment room, and is replicated by another set of three orthogonal lasers in the simulation room. Aligning external marks such as tattoos and symbols drawn with permanent ink on patients’ skin with the laser beams increases the reproducibility of patient positioning at each fraction. Immobilization devices are often used to facilitate the reproduction of patient position from the time of planning to the last treatment fraction\(^{14}\).
In image-guided radiotherapy (IGRT), the patient is imaged with a 3D cone-beam CT (CBCT) installed in the treatment room immediately before each fraction. Since tumors are generally not visible on CBCT images due to image contrast limitations, recognizable surrogates are used to represent the tumor position. Commonly used surrogates include natural anatomical landmarks such as bony structures and vascular bifurcations, or artificially implanted fiducial markers such as gold seeds for prostate cancers. Advancement in imaging technologies has enhanced soft tissue contrasts, allowing improved visualization of organs such as the liver on CBCT images. Consequently, the tumor-containing organ can also be used as a surrogate for the tumor. The CBCT images at each fraction are mapped onto the treatment planning image to align patient anatomies via online rigid image registration, which treats patient organs and structures as rigid bodies, without taking any change in shape and size into account\textsuperscript{15}. Errors in tumor positions identified from registration can be corrected by couch shifting. Tumor localization through rigid image registration assumes that the movement of the surrogates is exactly the same as the movement of the tumor, which is not always true\textsuperscript{13,15,16}. Alternatively, deformable image registration can be used to align CBCT images with the planning image to incorporate tissue deformations, recognizing that displacements of the surrogate and the tumor may be different. However, clinical implementation of deformable image registration is currently limited by its long computation time and demand for powerful computers. More details about deformable image registration will be discussed later.

During the course of treatment, tumors and healthy tissues may respond to radiation and subsequently shrink or expand, which also contribute to inter-fractional variations. Furthermore, this change in the geometry of patient anatomy can potentially alter the spatial relationship between the tumor and its surrogates\textsuperscript{17}. If the change is significant, the
treatment may need to be modified or re-planned.

3.2 Intra-fractional Variations

Motions due to physiological processes, predominantly respiration, cause intra-fractional organ displacements. In particular, the lungs and liver can be deformed by a few centimetres due to breathing, leading to potentially significant beam delivery errors. Organ and tumor movements due to respiration can be addressed by PTV margin expansion, image guidance, gated beam delivery technique, and breathing motion control\textsuperscript{18}.

The PTV margin ensures that the tumor is covered under a high dose level at all time. However, margins do not account for the movement of the normal tissue into and out of the treatment field. The amplitude of tumor displacement due to breathing can be measured with 4D CT or regular CT performed during breath-holding at inhalation and exhalation. A PTV can then be expanded to enclose the entire range of respiration-induced tumor motion\textsuperscript{19}. Although it is probably the simplest solution, increasing PTV margin causes more healthy tissues to be irradiated with high dose. Nevertheless, this approach is still often used when treating lung and liver cancers since the lungs and liver are considered parallel OAR.

Tumor displacements can also be addressed by image guidance, which requires imaging the patient with 4D CBCT at each fraction\textsuperscript{15}. The 4D CBCT images can be correlated with different phases of the respiration cycle. The image corresponding to inhale can be mapped with the image corresponding to exhale via deformable image registration, enabling characterization of a patient’s breathing motion at the time of treatment.

The third option to compensate for respiration-associated organ movements is to gate the
beam delivery at the same phase of every respiratory cycle, assuming the breathing motion is consistent over multiple cycles\textsuperscript{20}. However, a number of studies have pointed out the unpredictability of respiratory motion, particularly for individuals with pulmonary conditions such as asthma and lung cancers\textsuperscript{14}. Gated RT also imposes great technological challenges, as it requires highly precise timing and control mechanisms\textsuperscript{18}.

Another alternative is to control the magnitude of breathing motion. One method is to apply a compression plate onto a patient’s stomach to reduce the motion inside the abdominal cavity in the anterior-posterior (AP) direction\textsuperscript{14, 21}; another method is to let the patient wear a device called an active breathing control (ABC), which blocks the flow of air thus stopping the breathing motion at full exhalation/inhalation for radiation delivery; or, patients can voluntarily hold their breaths according to therapists’ instructions. The drawback is that breathing control techniques cannot be applied to a significant portion of patients due to communication barriers and breathing difficulties\textsuperscript{22}. 
4. Deformable Registration in MORFEUS and Elastic Properties of Soft Tissue

In contrast to rigid registration, which assumes the organs are stiff bodies whose shape and size do not change, deformable registration aims at predicting tumor displacements inside the organ based on measurable organ deformations in 3D. Common deformable registration techniques include similarity-based algorithms, fusion alignments, B-splines, thin-plate splines, finite element modeling (FEM), and others\textsuperscript{19}.

Our research group at Princess Margaret Hospital has developed MORFEUS, which is a biomechanics-based deformable registration platform that utilizes FEM to simulate the kinematics of a single organ or multiple organs\textsuperscript{23, 24, 11}. Biomechanics is a study that applies mechanical principles to investigate biological systems. Disciplines including thermodynamics, solid/fluid dynamics, classical mechanics, and material science are extensively involved in the study of biomechanics. FEM is a widely used mathematical tool in biomechanical research. By breaking a 1D, 2D, or 3D structure into an assembly of discrete elements and assuming continuity along the boundary between adjacent elements, FEM simplifies the process of solving theoretically an infinite number of partial differential equations that govern the dynamic behaviours at every point to the process of solving only a finite number of equations. Computational time and cost increase with the number of elements.

The module that performs deformable registration in MORFEUS is named rMORFEUS, where ‘r’ stands for registration. MORFEUS also has a number of other modules, the functions of which extend beyond, but are based on deformable image registration. Other MORFEUS modules will be described later. The process of deformation registration
performed in rMORFEUS is briefly described in the following example of registering the liver from its exhale position to its inhale position:

1) In the treatment planning system, the liver is contoured respectively on the primary image set (i.e. the exhale CT image) and the secondary image set (i.e. the inhale CT image).

2) Two mask files that define the exhale and inhale boundary of the liver are generated respectively from the two sets of contours, and are exported from the treatment planning system.

3) The two mask files are converted into two surface meshes which represent the liver at its exhale and inhale positions, respectively.

4) A rigid registration is performed first to provide a basic alignment of the primary (exhale) mesh to the secondary (inhale) mesh, based on the centre of mass (COM) of each structure.

5) The primary mesh is deformed into the shape of the secondary mesh through a guided surface projection method. The deformation of the surface is then set as the boundary condition of the subsequent finite element analysis (FEA).

6) The primary mesh is converted to a volumetric mesh of tetrahedral elements. This volumetric mesh is the FEM of the liver. The biomechanical properties of the liver are then assigned to the FEM.

7) The displacement at each node of the FEM can be calculated by solving the constitutive equations based on the boundary conditions derived from the surface
projection in step 5) and the biomechanical properties assigned to the FEM.

The result of deformable registration can be validated by comparing the calculated displacement of a fiducial marker or an anatomical landmark (e.g. a vessel bifurcation) with its measured displacement obtained from the primary and secondary image sets. Through repeated tests and refinements, rMORFEUS is able to achieve a registration accuracy of 2 millimetres or less\(^{11, 24}\).

Among the factors that can affect rMORFEUS’s calculation results, biomechanical properties have a particularly strong impact, since they define the mechanical responses of the tissue under physical stresses and the interactions between different parts of a biological system. The most important biomechanical properties include Young’s Modulus (E) and Poisson’s Ratio (v). Young’s Modulus represents the elasticity of the material, indicating the relationship between force and displacement. Poisson’s Ratio indicates the compressibility of the material. A perfectly incompressible material has the Poisson’s Ratio of 0.5, meaning that the volume of the material does not change under compression.

Most tissues are non-linear, although can be approximated as being linear elastic under small deformations usually in the order of millimetres. Some structures are highly anisotropic, meaning their biomechanical properties are different along different orientations. For example, long bones are very strong and able to bear heavy compressions in the direction of its longitudinal axis, but are much weaker in the cross section and do not have much resistance against bending moments. Most tissues such as the lungs, are also heterogeneous due to the vasculatures, the bronchial tree, and the presence of tumors\(^{25}\). Furthermore, in living organisms, tissues are constantly changing their structures, compositions, and
consequently material properties. Conditions such as extracellular ion concentrations, temperature, pH, and level of hydration, can substantially alter tissue properties, leading to significantly different material properties for the same tissue measured in vivo and in vitro, or simply at different times in vivo. The abovementioned factors in addition to inter-personal variations make accurate tissue property measurements a difficult task.26, 27

5. Soft Tissue Material Property Measurement

Since most biological tissues are heterogeneous, nonlinear, viscoelastic, and/or anisotropic, by principle, many material property parameters, including the Young’s Modulus, viscosity, hysteresis, Poisson’s Ratio, etc., are required to fully characterize a tissue. However in most cases, it is at least impractical to experimentally measure the values of all of these material properties. Therefore most soft tissue property measurement methods measure only a subset of all biomechanical properties, particularly the Young’s Modulus, because it can be used in the diagnosis of certain diseases such as breast cancer. Although a standard way of measuring soft tissue elasticity in vivo or in vitro has not been established yet, a number of techniques have been developed to accomplish this task. All techniques involve deforming the tissue in some way with a known or measured force or displacement, and detecting the response of the tissue to the applied deformation. Elastic property can then be quantitatively derived from the force-displacement data. Inter-individual variations in tissue properties partially contribute to the significant discrepancies between the elasticity measurements reported in different studies investigating the same organ. Therefore in medical applications, it is highly beneficial to be able to measure the tissue elasticity at the site of interest on individual basis to obtain patient-specific data.
Some popular techniques to measure the Young’s Modulus of soft tissues are briefly described below.

5.1 Indentation

Indentation is a frequently used technique to measure the Young’s Modulus of soft tissues. A popular setup consists of a probe, motion of which is usually driven by an actuator and controlled by a computer, and an electromechanical transducer. Egorov et al has developed a commercially available tissue elastometer that employs this setup. The elastometer is one of the first devices specifically designed for ex vivo measurement of biological tissue elasticity. As shown in Figure 1.3 below, the base of the elastometer is an electronic balance, which serves as both the object plate to place the specimen and a transducer to measure the force applied to the specimen. The height of the four legs supporting the balance can be individually adjusted to level the object plate. The indenter is a cylindrical probe with a rounded tip that has a diameter of 3.0 mm. The probe is driven by a linear actuator, the movement and position of which are controlled and monitored by a laptop. The actuator can provide a linear vertical motion at the speed of 0.05-0.1 mm/s in steps as small as 0.01 mm. When the probe deforms the surface of a tissue sample in each step, the balance measures the instantaneous reaction force to the precision of 0.1 mN, and the laptop collects the force-displacement data along the operation.
Figure 1.3. The Tissue Elastometer

1. The electronic balance; 2. The linear actuator; 3. The graphic user interface; 4. The cylindrical indenter with a rounded tip; 5. A test specimen on the object plate

Measurement results by the indentation technique largely depend on the physical boundary conditions of the specimen, including the size, shape, and confinements. Since it is unlikely to gain a precise understanding of these conditions at every measurement, most elasticity calculation algorithms are based on a biomechanical model which simplifies the boundary conditions to derive a mathematical relationship between force, displacement, and elasticity. For the model to be valid, however, the specimen must meet certain restrictions on its shape and dimension. The elastometer, for example, employs a deformation model of semi-infinite media to reflect the mechanical response of the specimen to the indentation. For the semi-infinite media model to be applicable, the elastometer requires the thickness and width of a sample to be at least twice and three times of the indenter diameter, respectively. Under these conditions, the behaviour of the specimen can be described by the following equation
for small indentations:

\[ E = \frac{3F}{\pi^2 RW} \]  

EQN 1.2

R is the radius of the indenter tip; F is the applied force; and W is the displacement the indenter applies to the sample surface. The Young’s Modulus is then calculated from the slope of the best-fit straight line in the linear region of the measured force-displacement curve\(^29\). The elastometer will be used in the present study for elasticity measurements.

The indentation technique is a fast and convenient way of measuring the Young’s Modulus of soft tissues. It is quantitative and usually does not require complicated test equipment, and can be applied in vivo or ex vivo. The indentation technique can also be used to investigate the heterogeneity of a tissue by taking measurements at different locations. In addition, stress relaxation can be tested by maintaining a constant displacement over a period of time. The shortcomings of the indentation method include the often imposed restrictions on sample dimensions, inadequacy in examining tissue anisotropies, and its invasiveness when used in vivo. Also, since only the local superficial modulus can be measured, it is difficult to acquire the elasticity profile inside the tissue\(^26, 28, 29\).

5.2 Compression/Elongation

The compression/elongation technique is adapted from the elasticity measurement of non-biological materials and is used almost exclusively ex vivo. During measurements, the tissue specimen, usually cut in a cylindrical shape to avoid irregular vertical cross sections, is placed between two flat plates that are typically aligned vertically. The specimen must be in full contact with both plates. Driven by a controllable actuator, one or both plates can move
linearly along the direction of alignment. Since the plates can be regarded as being completely rigid relative to the specimen, the amount of elongation or compression is determined from the distance the plate(s) travels through. A typical testing setup is shown in Figure 1.4:

![Image](image.png)

Figure 1.4. A typical tissue elasticity measurement setup for the compression/elongation technique

The compression/elongation test often serves as a reference when evaluating other material elasticity measurement techniques because of its accuracy and reliability. Viscoelasticity can also be studied by applying oscillatory forces at different frequencies to the specimen. The elastic properties of anisotropic materials can be measured by biaxial or multi-axial tests. The disadvantages of the compression/elongation technique include the application difficulty for in vivo measurements, the constraints imposed on the shape and size of the sample, as well as the inability to investigate tissue heterogeneities. In addition, as mentioned before, factors such as the level of hydration and chemical concentrations may greatly influence tissue properties. Therefore, to obtain knowledge on in vivo tissue properties from ex vivo measurements, the environment surrounding the specimen must be handled carefully to mimic the in vivo conditions as much as possible.
5.3 Aspiration

Aspiration, sometimes also called the pipette technique, is more recent than the indentation and the compression/elongation techniques. The force exerting device is a pipette, in which a partial vacuum is created to generate a suction force on the tissue surface when the pipette comes in contact with the tissue. A camera is usually used to view and record the deformation profile along the tissue surface. A pressure transducer is used to continuously monitor the pressure inside the pipette to precisely control the suction force\textsuperscript{27,32}. The aspiration technique and an example of its in vivo application are illustrated in Figure 1.5.

To calculate the Young’s Modulus, the tissue is usually represented by a particular constitutive biomechanical model, which defines the mathematical relationship between stress, strain, and the tissue’s material properties. A numerical model, often an FEM as shown in Figure 1.5 (c), of the tissue is generated, and the pipette’s internal pressure is applied to the FEM as the boundary condition. The inverse method is frequently used to solve for the model.
Figure 1.5. Illustration of the Aspiration Technique to Measure Tissue Elasticity in vivo

(a) In vivo measurement of the elastic property of a human liver; (b) The deformation of the liver surface due to the partial vacuum inside the pipette; (c) The FEM of the liver and the pipette to solve for the elastic property.

The aspiration technique is applicable for both in vivo and ex vivo tissue property measurements. It can be used to examine the viscoelasticity and nonlinearity of biological tissues, and the data acquisition time is relatively short. However, more complicated apparatus is required comparing with the indentation and compression/elongation methods. Computationally intensive numerical methods such as FEM are involved. And the aspiration technique is not effective in measuring anisotropic properties. Similar to the indentation technique, the aspiration method cannot measure properties deep inside the tissue.

5.4. Elasticity Imaging

Elasticity imaging takes advantage of modern medical imaging technologies, predominantly MRI and ultrasound. Structures with different elastic properties respond differently to the same physical disturbance, and this difference can be captured on medial images, such as MRI and ultrasound. A typical example of elasticity imaging is magnetic
resonance elastography, or MRE. An applicator delivers an oscillating force, either compressive or shear, at a frequency ranging from 1 Hz to 500 Hz to the tissue, generating a mechanical wave that propagates throughout the tissue. Meanwhile the tissue is imaged using a special motion detecting gradient sequence. Since the frequency and magnitude of the motion are already known, a strain map can be derived from the phase image.

An FEM of the tissue is almost always used to calculate the Young’s Modulus. The Young’s Modulus can be computed by either setting it as the unknown and directly solving for it, or using the more popular inverse method, in which the deformation is the unknown parameter. Young’s Modulus is obtained through iterations of computation that converge the calculated deformation to the measured value\textsuperscript{33, 35, 36}. Ultrasound is another imaging modality frequently employed in elasticity imaging techniques\textsuperscript{34}.

The biggest advantage of elasticity imaging is its non-invasiveness, because of which elasticity imaging is considered to have a great clinical application potential. In fact, studies have already demonstrated the effectiveness of MRE in diagnosing liver and breast cancers, since tissue stiffening, which can be detected by MRE, often occurs before the appearance of visible tumor mass. Elasticity imaging can also be used to study anisotropic tissues by changing the orientation of the applied force. However, the accuracy of its quantitative elasticity measurements is limited by achievable image resolution. Image elasticity is also more expensive than other tissue elasticity measurement techniques in terms of both hardware requirement (e.g. MR scanner) and computational cost\textsuperscript{33, 35, 36}.

6. Dosimetry in RT

Dosimetry involves the calculation and measurement of radiation dose, which ultimately
determines patient response and the outcome of the radiotherapy. Dosimetric verification is very important in conformal RT, which often includes steep dose gradients. If the delivered dose does not follow the planned distribution, the risk of insufficiently irradiating the tumor and overdosing the surrounding OAR increases, thereby compromises treatment outcome.\(^{37}\)

Portal images are frequently used for dosimetric verifications of IMRT. A radiographic device, which can be a fluoroscopic film or an electronic flat panel, is mounted on the gantry of the linear accelerator opposite to the treatment head.\(^{38}\) Prior to treatment, the plan is delivered without the patient. Each beam, which has its specific shape and intensity, is projected onto the planar imaging device. The final image is compared against the dose projection on the same plane estimated by the treatment planning software.\(^{39}\)

Dosimetry is also critical in quality assurance (QA) checks on RT treatment units. Dose measurement tools include ionization chambers for absolute point dose measurement, fluoroscopy films for relative plane dose measurement, radiographic flat panel, which is a matrix of radiosensitive diodes, for absolute plane dose measurement, and the least common gel dosimeters for relative volumetric dose measurement.\(^{38, 39}\)

### 6.1 3D Gel Dosimetry

Although both treatment planning and delivery are carried out in three-dimensions, most dose measurement devices for clinical use are not. Most volumetric dose distribution maps are calculated using complicated algorithms such as convolution-superposition or the Monte Carlo method to simulate particle-media interactions along the beam path. Gel dosimetry provides the opportunity of quantitatively measuring the actual dose distribution in 3D, and
offers a tool to experimentally validate dose calculation algorithms. The clinical implementation of gel dosimetry, however, is impeded by its laborious manufacturing process, non-reusability, and complex dose measurement procedures. There are three main types of gel dosimeters: ferrous-sulphate, polymer-based, and leuco dye-based. The working principle of all three types is that ionizing radiation induces detectable chemical reactions in the dosimeter.

**Ferrous-sulphate dosimeter**, also known as the Fricke gel, was developed from the Fricke solution, which was used in radiation dosimetry since more than 60 years ago. When being irradiated, the ferrous (Fe$^{2+}$) ions (usually from ferrous ammonium sulphate) dispersed throughout the Fricke solution are oxidized to ferric (Fe$^{3+}$) ions. In 1984, Gore et al first proposed combining the Fricke solution with MRI to make 3D dosimetry possible. Since iron is ferromagnetic, the conversion from Fe$^{2+}$ to Fe$^{3+}$ alters the magnetic resonance relaxation properties of the surrounding water molecules, which is reflected in the change of local longitudinal relaxation constant, R1. The increase in R1 after irradiation is proportional to the Fe$^{3+}$ ion concentration, which, in turn, is proportional to the absorbed radiation energy. Therefore Gore et al demonstrated that under certain dose limits, a linear R1-dose plot for a Fricke solution could be generated if the R1 is measured after the solution is irradiated with a known dose. For solution preparation, it was noted that exposure to lights should be avoided before irradiation since visible lights, also a form of electromagnetic waves, may initiate undesirable oxidation reactions.

It was noted that the aqueous Fricke solution could not retain the spatial dose distribution information due to ion diffusions. Consequently, Fricke gel that uses gelatin or agarose as the bulk material was developed. With some improvement on the ion diffusion issue, spatial
information would still be lost over time. Therefore MRI must be performed in few hours after irradiation. Later studies have discovered that using polyvinyl alcohol (PVA) as the bulk material and including additives such as formaldehyde in the Fricke gels can significantly reduce ion diffusive activities\(^42\). Sometimes xylenol orange, the colour of which changes from purple to orange by forming a metallo-organic complex with \(\text{Fe}^{3+}\) ions, is added to the Fricke gel to inhibit ion diffusion. Dose distribution can then be derived from the change in optical density, which is measured by spectrophotometer\(^43\).

**Polymer-based dosimeters** are currently the most commonly used type of 3D gel dosimeters. They were developed to address the problem of spatial dose information loss of Fricke gels. In polymer-based gels, monomer molecules are dissolved throughout the bulk material\(^40,\,44-46\). Through a series of radiation-initiated reactions, the monomers assemble into long plastic polymer chains. The general reaction mechanism is illustrated below\(^40\):

\[
\begin{align*}
\text{Initiation, free radicals generated:} & \quad H_2O \rightarrow 2R\bullet, \ R\bullet = H\bullet \text{ or } HO\bullet \\
\text{Propagation:} & \quad R\bullet + M_n \rightarrow R\bullet M_n, \ 1 \leq n, m \\
R\bullet M_n + M_m & \rightarrow R\bullet M_{n+m} \\
\text{Termination:} & \quad R\bullet + R\bullet \rightarrow I, \ I = H_2, H_2O, \text{ or } H_2O_2 \\
R\bullet + R\bullet M_n & \rightarrow I + M_n \\
R\bullet M_n + R\bullet M_m & \rightarrow I + M_{n+m} \\
R\bullet M_n + R\bullet M_m & \rightarrow I + M_n + M_m 
\end{align*}
\]

The degree of polymerization depends on the amount of received dose. The polymer product of the above chain-growth polymerization affects the mobility of the surrounding water molecules, thus changes the local transverse MR relaxation constant, \(R_2\). Since \(R_2\)
increases with the delivered dose, an R2-dose plot can be generated by measuring the R2 of the dosimeter. Polymer-based gels can be further categorized according to the monomers used. The two most common types are poly-acrylamide gelatin (PAG) gel, which uses acrylamides as the radiation sensitizing monomer, and methacrylic acid gelatin (MAG) gel, which uses the less toxic methacrylic acids\textsuperscript{40,46}.

The manufacturing process of polymer-based gels used to be very laborious and complicated. Early gels must be made in a special glove box purged with nitrogen, because the monomers are toxic, and the oxygen in the air neutralizes free radicals, thereby quickly terminates chain growth after radiation has initiated the polymerization process. The gel needed to be stored in an airtight container immediately after fabrication before being moved out of the glove box to avoid contact with oxygen. Therefore the earlier polymer-based gel dosimeters are also referred to as hypoxic (low oxygen) gels. In 2001, Fong et al proposed a new polymer gel composition, which incorporates the antioxidant ascorbic acid (vitamin C), copper (II) sulphate, and hydroquinone. Ascorbic acid is able to bind to the free oxygen molecules in the gel, copper sulphate can catalyze the oxygen binding process, and hydroquinone can facilitate the polymerization process. This new composition eliminated the necessity of using a glove box and enabled polymer-based dosimeters to be fabricated under normal atmospheric conditions\textsuperscript{47}. A number of other antioxidants have been investigated in subsequent studies, and tetrakis (hydroxymethyl) phosphonium chloride (THP) has been shown to be the most effective antioxidant. Moreover, THP has also been shown to promote the polymerization process, thus increases the dosimeter’s sensitivity to ionizing radiations. More recent gels containing antioxidants or oxygen scavengers are referred to as normoxic (normal oxygen level) gels\textsuperscript{40,46}. However, normoxic gels still need to be kept in airtight
containers since the antioxidants will eventually deplete. Similar to Fricke gels, all polymer-based gels, hypoxic or normoxic, should be preserved in dark since light can initiate undesired polymerization.

Leuco dye-based dosimeters are the most recently developed type of 3D gel dosimeters. Leuco dye is a photochromic material which is normally transparent, but becomes coloured when exposed to ionizing radiation. Therefore the received dose can be measured by using optical devices such as optical CT and charge coupled device (CCD), to detect the change in dosimeters’ light scattering or absorbing properties. A commercially available dosimeter PRESAGE dopes leuco malachite green throughout a bulk of polyurethane, which is a rigid plastic. PRESAGE has low toxicity, and is not sensitive to ambient oxygen. However, since plastic fabrication is required, it is not practical to manufacture PRESAGE in hospitals or clinics. Also, PRESAGE is less tissue equivalent comparing with Fricke gels and polymer-based gels37.

All 3D gel dosimeters, ferrous sulphate, polymer-based or leuco dye-based, offer a means of relative volumetric dose measurements that requires calibration to generate a dose-response curve that reflects the mathematical relationship between dose and the dose reflecting parameter: R1, R2 or light scattering property. Since inter-batch variation in gel composition can significantly compromise measurement reproducibility, calibration is required for every batch of dosimeters. A dosimeter’s sensitivity to radiation is represented by the slope of the dose response curve40, 44-46.

7. Including Organ Movement and Deformation into Dose Calculation

It has been widely acknowledged that organ movements and deformations can introduce
errors and uncertainties in beam targeting in radiotherapy. Advancement in imaging technology and image registration algorithms has allowed quantitative assessment of these errors. In particular, studies have demonstrated both analytically and experimentally that omitting deformations may result in errors in tumor position predictions. However, dose calculation and verification are both performed under static conditions without taking organ motion and deformation into account. There also lacks a method to verify if the dose absorbed by the tissue actually equals to the planned dose. One possible source of discrepancies is that the surrogates used to align patient anatomy at each fraction of treatment with that at the time of planning do not always accurately represent the tumor position. Therefore, tumor localization and beam targeting errors can occur. Combined with infra-fractional organ movements due to respiration, the tumor can move out of the high dose area, leading to insufficient irradiation of the PTV, while overdosing the surrounding normal tissue. Another factor may contribute to dose error is that physiological motions can compress and stretch organs, leading to temporal changes in tissue densities, which, in turn, affect dose absorption. The abovementioned factors all point out the necessity to consider organ motion and deformation in dose calculation.

Therefore, our research group has developed a 3D dose accumulation algorithm named dMORFEUS based on the rMORFEUS deformable registration technique to incorporate organ and tumor deformation\textsuperscript{48,52}. The goal of the presently proposed study is to experimentally validate this algorithm. Respiratory motion is the focus of the study since it is the main source of intra-fractional motions particularly for the liver and the lungs, but is not considered in clinically used dose calculation systems. Although some studies have attempted to investigate the effect of respiratory motion on dose distribution, most of them
simulated the motion as rigid body motions only. The proposed study addresses this shortcoming by employing a more realistic physical simulation of respiratory motion. 3D gel dosimeters will be used to obtain a true volumetric measurement of dose distribution.

8. Overview of Thesis

The overall objective of this project is to experimentally validate the dMORFEUS dose accumulation algorithm. The hypothesis of the project is that validation of including deformation in dose accumulation can be achieved by using a deformable 3D gel dosimetry phantom. This hypothesis has been investigated through three specific aims.

Specific Aim 1: Establish a suitable deformable gel dosimeter.

Existing gel dosimeter fabrication techniques are modified to enable a deformable dosimeter with accurate spatial and dosimetric capabilities.

Specific Aim 2: Design and construct a portable actuation device that can deliver an oscillatory motion similar to respiration to deform the gel dosimeter.

To study the effect of respiratory motion on dose delivery, deformable gel dosimeters were irradiated while being deformed in a similar way the liver is due to respiration. Thus, an actuation device that can deliver a respiration-mimicking motion to the dosimeter was designed and constructed. The device is also portable for convenient transfer to the treatment couch.

Specific Aim 3: Compare the dose calculated by Pinnacle and accumulated in dMORFEUS with that measured with gel dosimeters.
The dose measurement performance of the gel dosimeters was first evaluated by comparing the measured dose with the dose computed in Pinnacle under static conditions. The dose accumulation algorithm of dMORFEUS was then validated by comparing the dMORFEUS dose with the dose measured with gel dosimeters under the condition of deformation.
CHAPTER 2: Development of a Deformable 3D Gel Dosimeter
1. Introduction

1.1 Gel Attributes

The criteria of an ideal 3D gel dosimeter for this study are that it should be deformable, easy to fabricate, safe to handle, reflective of true spatial dose distribution, and able to preserve this information over time. Unfortunately, literature searches did not find any readily available dosimeter that satisfies these criteria: Fricke gels and polymer-based gels are difficult to handle due to their toxicity or sensitivity to light or oxygen, while the leuco dye-based dosimeters are rigid and undeformable. Polymer-based gels were chosen for the following reasons:

1) Polymer-based gels are able to maintain spatial dose information over time.

2) It is possible to manufacture deformable polymer-based gels.

3) The materials for making the gels are readily available at Princess Margaret Hospital.

The biggest hindrance in utilizing polymer-based gels is that they are conventionally kept in rigid, airtight containers to avoid contact with oxygen, but at the same time this makes it impossible to deform the gels. Therefore, a new containment method, which allows motions to be applied to the gels, must be developed. Glad plastic food wrap is made with low-density polyethylene (LDPE), which has low oxygen permeability and can serve as a flexible oxygen barrier when wrapped around the gel.
1.2 Gel Composition

The materials for making polymer-based gel dosimeters are: gelatin powder, methacrylic acid (MAA), antioxidant (THP), and de-ionized water. The effect of increasing the concentration of each material, other than water, on dosimeter properties is summarized in Table 2.1 below:

<table>
<thead>
<tr>
<th>Dosimeter Materials</th>
<th>Toxicity</th>
<th>Sensitivity to radiation</th>
<th>Oxygen inhibition</th>
<th>Dose measurement stability after irradiation</th>
<th>Stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin</td>
<td>Unaffected</td>
<td>Increase</td>
<td>Unknown</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>MAA</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
<td>Unaffected</td>
<td>Unknown</td>
</tr>
<tr>
<td>THP</td>
<td>Unaffected</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Unaffected</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 2.1. Effect of Increasing the Concentration of Each Material on Dosimeter Properties

Dose measurement stability after irradiation refers to the change in the R2-dose plot if multiple MR scans are performed at different times after irradiation. The study by De Deene et al shows that for polymer-based gel dosimeters, both the intercept and the slope of the R2-dose plot change with time after irradiation. Therefore, all dosimeters of the same study have to be manufactured, irradiated, and imaged at the same time to generate reproducible and comparable measurement results.

2. Materials and Methods

2.1 Gel Composition and Fabrication

From literature review and experience gained from preliminary tests, a gel dosimeter suitable for the application in this project has been developed. The gel is i) deformable, ii) relatively
immune to oxygen inhibition, and iii) sensitive to ionizing radiation. The composition of the gel dosimeter is:

- Gelatin (300 Bloom, Type A, Sigma): 8 (w/w) %
- MAA (99%, Aldrich): 5 (w/w) %;
- THP (80% H2O solution, Aldrich): 50 mM;
- De-ionized water

8% gelatin is the most commonly used gelatin concentration seen in literature, and is also the optimal concentration concluded from preliminary tests. Lower gelatin concentration yield gels that are too soft to maintain their physical shapes over the course of an experiment, while it would be difficult to completely dissolve the gelatin powder once the concentration is beyond 8%.

5% MAA is also commonly used in literature. Preliminary tests have shown that MAA concentration is positively correlated with gel sensitivity to radiation dose. However, it is reported in literature that the acidity of MAA may affect the gelation process of the gelatin molecule, which may weaken the physical structure of the gel dosimeters. Therefore, a higher MAA concentration was not used.

The THP concentration of 50 mM is higher than most other studies published in literature, which generally use 20 mM or less. Since the gels were enclosed in plastic wraps and sealed with tape, which together form a poorer oxygen barrier than rigid plastic or glass containers used in other studies, the concentration of THP, which is the oxygen scavenger, was increased to compensate for the extra oxygen infiltration.
The gel fabrication process is described as follows:

1) Gelatin powder was thoroughly soaked in 90% of the water, and the mixture was then stirred and heated to 50°C for 45 to 60 minutes to completely dissolve the gelatin.

2) MAA and THP were mixed in the remaining 10% of the water.

3) Meanwhile, the temperature of the gelatin solution was lowered to 35°C to preserve the antioxidant potency of THP.

4) The two solutions were combined and stirred for another two minutes.

5) The mixture was poured into paper coffee cups, which were in turn, put into high-density polyethylene (HDPE) cylindrical wide mouth jars that are 76 mm in height and 73 mm in diameter. The mixture was then stored in refrigerator at 4°C for 8 to 10 hours for the gelatin to solidify.

6) The paper cups were peeled off the gels, which were immediately re-sealed with plastic wraps and tapes.

The gel-making process was carried out in a fume hood due to the toxicity and corrosiveness of MAA and THP. Steps involving MAA must be performed in a dark environment to avoid polymerization triggered by visible lights.

The biggest challenge in the gel manufacturing process was to develop a method to remove the gel from its mould without damaging the gel. After trying various ways, it has been found that paper coffee cups could serve as ideal moulds. Because of their slippery polyethylene inner linings, paper cups could be easily torn off to obtain gel dosimeters with a smooth
The disadvantage, however, was that because paper cups do not effectively block air out, some oxygen infiltration would inevitably occur along the periphery of the gels.

2.2 Reproducibility Study

A study was carried out to evaluate the reproducibility of using gel dosimeters to measure radiation dose.

2.2.a Experiment Procedure

Gel Fabrication:

Six gels were manufactured in the same batch. Instead of using paper cups, the gels were all moulded and kept in the HDPE wide mouth jars.

Three gels denoted RS (reproducibility study) -1, RS-2, and RS-3, uniformly irradiated with 100 cGy, 250 cGy, and 400 cGy respectively, were used to generate the R2-dose calibration curve. The other three gels, denoted RS-4, RS-5, and RS-6, were irradiated with a conformal treatment plan consisting of 18 beams and with a prescription of 400 cGy to the centre.

The treatment design of the six gel dosimeters is summarized in Table 2.2:

<table>
<thead>
<tr>
<th>Gel</th>
<th>RS-1</th>
<th>RS-2</th>
<th>RS-3</th>
<th>RS-4</th>
<th>RS-5</th>
<th>RS-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Calibration</td>
<td></td>
<td></td>
<td>Test the reproducibility of dose measurement across gels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of Deformation Applied</td>
<td>No deformation applied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Plan</td>
<td>100 cGy uniform dose</td>
<td>250 cGy uniform dose</td>
<td>400 cGy uniform dose</td>
<td>18-beam conformal plan delivering 400 cGy to the centre of gel</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2. Treatment Design for the Six Gel Dosimeters Used in the Reproducibility Study
Pre-treatment CT Simulation:

To achieve uniform dose distribution, RS-1, RS-2, and RS-3 were treated inside a filled water tank. Therefore, to accurately calculate dose in a commercial radiation therapy treatment planning system (Pinnacle, v7.6, Philips Medical Systems, Madison, WI, USA), RS-1 was imaged inside the water tank on a CT simulator to provide the planning image for all three calibration gels. Since all gels had been produced in the same batch and were contained in identical jars, the CT image of one gel was deemed sufficient to represent all three gels. Because RS-4, RS-5, and RS-6 were treated without the water tank, RS-4 was imaged with CT to generate the planning image for these three gels. Both CT images had the resolution of $0.3 \times 0.3 \times 2 \text{ mm}^3$.

Each of the six gels had three external markers to help reproduce gel positions from the CT simulator to the treatment couch, and to the MR simulator.

Treatment:

All gels were treated on a clinical linear accelerator (Elekta Synergy S, Elekta Oncology Systems, Crawley, UK) three days after the pre-treatment CT simulation. Each gel was first positioned by aligning the external markers with in-room laser beams. A kV cone-beam CT (CBCT) image was then taken and registered with the corresponding planning image. The gel position was subsequently adjusted by couch shifting.

MR Imaging:

The MR image was acquired two days after the treatment on a clinical MR simulator (GE Signa 1.5T) using a birdcage transceiver head coil. Since positioning techniques such as
CBCT and couch shifting are not available on the MR simulator, gels were carefully positioned using the in-room laser beams.

A magnetization-prepared spiral imaging method, termed T2-prep, was used to measure the T2 (and thus R2) values of the gel\textsuperscript{54,55}. It is a time-efficient imaging method for volumetric imaging, yet T2 contrast development is robust to characteristic uniformities of both the radio-frequency and static field at 1.5 Tesla. The T2-prep method has been initially for accurate and precise T2 quantitation for vascular oximetry and cardiac measurements.

The T2-prep sequence consists of three segments:

1) A magnetization preparation interval to develop T2 contrast robustly without spatial selection. A non-selective composite $90_x (360_x, 270_x, 90_y)$ pulse rotates the spins to the transverse plane, followed by a MLEV refocusing train of composite $90_x, 180_y, 90_x$ pulses. The duration of the refocusing train is the predominant determinant of the echo time. The T2 contrast is then restored to the longitudinal axis by a composite $90_x (45_x, 90_y, 90_x, 45_y)$ pulse, for temporary storage before imaging.

2) The imaging interval. Imaging uses a spectral-spatial excitation pulse for slice-selection, and spiral gradient waveforms for spatial encoding. For each repetition time (TR), one spiral trajectory in K-space for one TE is filled, so that the total imaging time is proportional to the number TEs and the number of spiral interleaves. This RF and spiral gradient waveform combination is applied serially for spatial encoding of multiple slices of a volumetric acquisition without additional cost to scan time.
3) Longitudinal recovery interval. After completion of imaging, a 90° non-selective excitation pulse and a spoiler gradient is applied three times with very short intervals in between to null any residual longitudinal and transverse magnetization. Longitudinal magnetization then regrows for an interval with is approximately the TR less the combined duration of the echo time and imaging interval. The delay to the magnetization-reset pulse is modulated to ensure a constant period of longitudinal recovery despite the variable echo time of the T2 acquisition. The imaging parameters used were:

- TE: 3.2, 21.8, 40.5, 77.8, 152.4, and 301.7 ms
- TR: 5000 ms
- Number of Excitations (NEX): 4
- K-space: 1.5 × 1.5 × 2 mm³ resolution, spiral trajectory consisting of six 2600 interleaves
- Field of View (FOV): 160 × 160 mm²
- Total Acquisition Time: 11 to 12 min

2.2.b R2-Dose Calibration

The six echo times generated a set of six images of each axial plane. The T2 value of a voxel was obtained by fitting the greyscale intensities at that voxel in the set of axial images to a mono-exponential decay function:

\[ I(t) = I_o \exp\left(-\frac{t}{T2}\right), \]

EQN 2.1

where \( t \) is the time after the excitation pulse, \( I \) denotes the pixel intensity, and \( I_o \) denotes the theoretical signal intensity immediately after the excitation pulse. Once the T2 distribution was generated, R2 could be easily obtained by taking the reciprocal of T2.
The R2 maps of the gels were then imported into Pinnacle and registered with the corresponding treatment planning images. That is, the R2 maps of RS-1 to RS-3 were registered with the CT image of RS-1; and the R2 maps of RS-4 to RS-6 were registered with the CT image of RS-4. This step was to correct the positioning error on the MR simulator.

To obtain the R2-dose calibration curve, ten regions of interest (ROIs) were selected at different locations on the planned dose grid of each calibration gel dosimeter. The mean volume of the ROI is 90 mm$^3$ (ranging from 78 to 103 mm$^3$). The minimum, maximum, mean, and the standard deviation of the dose values in each ROI were calculated. The same set of ROIs was propagated to the R2 map of each corresponding calibration gel. Again, the minimum, maximum, mean, and standard deviation of the R2 values in each ROI were obtained. In this way, each ROI produced one point on the R2-dose calibration curve. A linear regression was performed to derive the mathematical relationship between R2 and dose. Studies have discovered that for MAA-based polymer gel dosimeters, the R2-dose relationship is best described by a biexponential function, but for low doses ($\leq 5$ Gy), the relationship can be satisfactorily approximated as a linear one. The generated calibration curve was then used to convert the R2 maps of RS-4 to RS-6 into dose measurements.

2.2.c Evaluation of Dose Level Measurement

Preliminary tests have shown that for deformable gels enclosed in plastic wraps, the minimum dose between 100 to 150 cGy was required to initiate gel response in the peripheral regions due to oxygen infiltration. Although oxygen penetration was not a concern for gels contained in airtight HDPE jars, for the purpose of consistency, all dose comparisons and analyses were performed only in regions with a reference dose of at least 200 cGy. In this
case, the planned dose was the reference against which the gel dose was evaluated. Therefore, the two dose distributions were compared only in regions with a planned dose greater than or equal to 200 cGy. Since the planned dose grids had the resolution of \(2\times2\times2\ mm^3\), while the resolution of the measured dose distributions was \(0.625\times0.625\times2\ mm^3\), the measured dose distributions were first down-sampled to match the resolution of the planned dose grid. Then for each of RS-4 to RS-6, a voxel-by-voxel comparison between the planned and measured dose distributions was carried out to evaluate the difference in dose levels at each voxel. The percentage dose difference at each voxel was also calculated using the following formulae:

\[
\%\ Dose\ \ Difference = \frac{\text{Pinnacle\ Planned\ Dose} - \text{Gel\ Dose}}{\text{Pinnacle\ Planned\ Dose}} \times 100\%
\]

EQN 2.2

2.2.d Evaluation of Spatial Distribution Measurement

A 3D dosimeter should not only accurately measure the amount of dose being delivered, but should also accurately reflect the spatial distribution of the delivered dose. To evaluate the performance of the gel dosimeters in measuring spatial dose distribution, four pairs of isodose surfaces at 250 cGy, 300 cGy, 350 cGy, and 400 cGy were extracted from both the planned dose grid and the measured dose grid for each of RS-4 to RS-6. Each pair of isodose surfaces was converted into surface meshes of 2 mm triangular elements. The average spatial distance between the corresponding gel isodose surface and the planned isodose surface was computed using finite element analysis methods in MORFEUS. This was analogous to the DTA tool frequently used in IMRT dosimetric verification.
2.2.e The 2%/2mm Test

A third method to evaluate the gel dosimeters’ performance in 3D dose measurement combines dose difference comparison and spatial distribution comparison. It is a pass-fail test and was inspired by the 2%/2mm gamma criterion commonly used in IMRT dose verification. Let the dose value at a voxel A in the gel dose grid be \( D_g \). In the Pinnacle planned dose grid, if a voxel B that had a dose value \( D_p \) such that \( 98\% D_p \leq D_g \leq 102\% D_p \), could be found within the 2 mm neighbourhood of voxel A, then voxel A in the gel dose grid was deemed to pass this test. If such a voxel B could not be found in the Pinnacle dose grid, then voxel A was deemed to fail the test. After examining every voxel in the gel dose grid, a pass-fail binary map was generated for each control gel dosimeter, where one represented pass and zero represented fail. The percentage of voxels that have passed the test was also calculated.

3. Results and Discussion

3.1 Reproducibility Study

3.1.a R2-Gel Calibration

The R2-dose calibration curve for the reproducibility study is shown below:
The error bars reflect the standard deviation in R2 value in the ROIs. $R^2 = 0.99$ shows that the R2-dose relationship could be well described by a linear equation.

3.1.b Evaluation of Dose Level Measurement

An axial snapshot of the Pinnacle planned dose, the measured dose, and the dose difference between the two, is shown below for each of RS-4, RS-5, and RS-6. The region over which the comparison between Pinnacle dose and gel dose was performed is outlined in black on each snapshot. For each gel, the two histograms showing the dose difference and percentage dose difference between the planned and measured dose distributions are also displayed. On each histogram, the mean and standard deviation (SD) of the dose difference or percentage dose difference, as well as the percentage of voxels falling in the range of mean ± 1SD, are also displayed.
Figure 2.2. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Planned Dose Calculated in Pinnacle and the Dose Measured by RS-4.

(a) Axial snapshots of the static Pinnacle dose, the RS-4 gel dose, and the difference between the Pinnacle and the gel doses. The region over which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and gel dose for RS-4.
Planned Dose (cGy)  

RS-5 Gel Dose (cGy)

Planned Dose – RS-5 Gel Dose (cGy)

(a)
Figure 2.3. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Planned Dose Calculated in Pinnacle and the Dose Measured by RS-5.

(a) Axial snapshots of the static Pinnacle planned dose, the RS-5 gel dose, and the difference between the Pinnacle and the gel doses. The region over which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and gel dose for RS-5.
Planned Dose (cGy)  RS-6 Gel Dose (cGy)

Planned Dose – RS-6 Gel Dose (cGy)

(a)
Figure 2.4. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Planned Dose Calculated in Pinnacle and the Dose Measured by RS-6.

(a) Axial snapshots of the static Pinnacle planned dose, the RS-6 gel dose, and the difference between the Pinnacle and the gel doses. The region over which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and gel dose for RS-6.
The axial snapshots of the gel dose indicate the presence of significant MR image noises. Literature suggests that MR noise is a major source of dose measurement errors and uncertainties in gel dosimetry. Therefore, the noise issue needs to be addressed in subsequent studies. The signal to noise ratio (SNR) in the MR images was measured by dividing the mean intensity at the centre of the gel by the standard deviation of the background noise. The average SNR of the MR images is about 110 in the reproducibility study.

According to the histograms, the mean dose difference between the planned distribution calculated in Pinnacle and the distribution measured with gel dosimeters is small that the absolute mean dose difference is less than 5 cGy and the mean percentage dose difference is less than 3%. However, the standard deviations of dose difference and percentage dose difference are relatively large with the average values of 22.17 cGy and 8.15%, respectively. The large standard deviations observed for all three gels could be attributed to MR image noises.

3.1.c Evaluation of Spatial Distribution Measurement

For each gel, the results of comparing the four pairs of isodose surfaces were obtained and reported in the tables below. For each pair, the mean and standard deviation of the distance between the two surfaces, the absolute maximum distance, and the absolute 95-percentile distance between the two surfaces in the left-right (LR), anterior-posterior (AP), and superior-inferior (SI) direction are shown. Vector refers to the magnitude of the net displacement from one point on the gel isodose surface to the corresponding point on the Pinnacle isodose surface.
Table 2.3. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the Static Pinnacle Dose and the Dose Measured by Gel RS-4.

<table>
<thead>
<tr>
<th>Metric</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
<th>Vector [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>-0.01</td>
<td>-0.02</td>
<td>0.00</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>0.11</td>
<td>0.09</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>abs_Max</strong></td>
<td>0.54</td>
<td>0.51</td>
<td>0.20</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>abs_95thP</strong></td>
<td>0.27</td>
<td>0.21</td>
<td>0.09</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Table 2.4. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the Static Pinnacle Dose and the Dose Measured by Gel RS-5.

<table>
<thead>
<tr>
<th>Metric</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
<th>Vector [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>0.01</td>
<td>0.00</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>0.05</td>
<td>0.04</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>abs_Max</strong></td>
<td>0.31</td>
<td>0.18</td>
<td>0.14</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>abs_95thP</strong></td>
<td>0.12</td>
<td>0.10</td>
<td>0.07</td>
<td>0.16</td>
</tr>
</tbody>
</table>
An interesting observation from the tables above is that the 95-percentile distance tends to be significantly less than the absolute maximum distance. This can also be interpreted as an effect of the relatively high noise level in the gel dose map, which would cause an irregular isodose surface with abrupt dents or spikes on the surface. The distance between the points at these locations and the corresponding points on the Pinnacle isodose surface would be unusually large. In this scenario, the 95-percentile distance would be a more appropriate indicator of the true maximum distance between each pair of isodose surfaces. In general, the 95-percentile distances are within 4 mm, which is the dimension of 2 voxels in the dose grids.
3.1.d The 2%/2mm Test

The passing rate of voxels in the ROI (i.e. the region in the planned dose grid that has a dose value of at least 2 Gy) in the 2%/2 mm test for each gel dosimeter is summarized in the table below:

<table>
<thead>
<tr>
<th>Criterion 2%/2mm</th>
<th>RS-4</th>
<th>RS-5</th>
<th>RS-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%/2mm</td>
<td>66.67%</td>
<td>69.33%</td>
<td>63.43%</td>
</tr>
</tbody>
</table>

Table 2.6. The 2%/2 mm Passing Rate of the Voxels in the Region with a Pinnacle Dose of \( \geq 200 \) cGy for Gels RS-4, RS-5, and RS-6

The passing rates for the three gels are comparable, with RS-5 having the highest passing rate and RS-6 having the lowest. This is consistent with the dose difference histograms displayed in Section 3.1.b, which show that RS-5 has the smallest mean and standard deviation of dose difference, while RS-6 has the largest mean and standard deviation.

The investigators believe that improving SNR in the MR images would increase the passing rate, since studies have shown that the gamma index, which is equivalent to the 2%/2mm test used in this study, is highly sensitive to image noises.

4. Conclusion

The issue of noises in MR images has been identified in the reproducibility study. Therefore, the MR imaging parameters need to be further optimized to achieve a higher SNR. Nevertheless, the three gels have shown very similar responses to the same treatment plan.
Therefore, it can be stated that gel dosimeters can generate reproducible dose measurement results.
CHAPTER 3 : Design and Construction of an Actuation Device
1. Introduction

The actuation device delivers periodic motions, similar to breathing motion, to deform the gel dosimeters. One required specification of the system is MR compatibility, because the same actuation system is also used in a separate research project, in which the device is placed inside a 7-tesla micro-MR scanner. Additional criteria on the device specifications include the ability to deliver motions at 15 to 20 revolutions per minute (rpm), corresponding to normal breathing frequencies; the ability to provide enough force to deform the dosimeters by up to 2 cm, representing liver motion due to respiration; and operation stability. Portability is also required for the actuation system, so that it can be transferred to RT treatment units. The system must be able to support itself so that it can be easily set up on the treatment couch.

2. Materials and Methods

The non-magnetic ultrasonic motor USR60-E3N from Shinsei Corporation, Japan, was selected to drive the actuation system, since it meets all the criteria described above. The external control circuit for the motor has been constructed to allow the users to adjust the direction and speed of the output rotation from 15 rpm to 150 rpm. The mechanical apparatus described in the paper by Samani et al has been adapted in the present study to convert the output rotation to periodic linear motion. The actuation system is depicted in Figure 3.1. below:
Figure 3.1. Picture of the Actuation Device Used to Apply Breath-Mimicking Motion to Deform Gel Dosimeters. In particular, the sample chamber and the motor are illustrated in more details.

As illustrated in Figure 3.1., the actuation device is 120 cm in length and 22 cm in height. The sample chamber in which dosimeters are placed is attached at one end of the device, and the motor mounted on the other end. The device can be divided into four sections in length by three vertical plates (highlighted with white rectangles in Figure 3.1). Each plate has a
hole at the centre that is just big enough to allow the main shaft that connects the motor and the piston to pass through. In this way, the motion of the shaft is limited in the horizontal direction only. The shaft consists of two pieces that are screwed together. The shaft length can be adjusted by up to 4 cm depending on the amount of threaded section being used to connect the two pieces. The piston is attached tightly on one end of the main shaft. The other end of the main shaft is connected by a rotating joint to a disc firmly fixed onto the motor shaft. Holes of various distances (0.5, 1, 1.5, 2 and 2.5 cm) from the centre are drilled on the disc. By changing the hole to which the main shaft is attached, the magnitude of the motion can be adjusted from 0.5 to 2.5 cm in increment of 0.5 cm.

The actuation device is portable and can be easily set up on treatment couches and MR simulators. Other than the motor, the entire actuation device is made of non-magnetic plexiglass.

3. Results

The performance of the actuation system has been evaluated in three aspects. The first was the output torque of the motor. It has been demonstrated that the motor was able to provide enough torque to deform the gel dosimeters used in this project by up to 2 cm. The second aspect being evaluated was the frequency range of the linear motion. A pressure transducer that is used to monitor small animals’ respiration during MR imaging was used to monitor the frequency of the delivered motion. It was shown that the motor could deliver motions at any frequency between 0.1 Hz (6 rpm) and 2.5 Hz (150 rpm), which was the desired frequency range for this project. The third aspect of the actuation device to be tested was operation stability, and it was demonstrated with the pressure transducer that the motor could
maintain the motion at any selected frequency for at least 20 minutes, showing excellent reliability.

4. Conclusion

An actuation device has been successfully designed and constructed. The device satisfies all the design specifications, including portability, MR compatibility, and the ability to deliver motions at the magnitudes and frequencies of natural breathing. Testing also proves excellent reliability of the device in delivering consistent motion for more than 20 minutes.
CHAPTER 4 : Evaluate dMORFEUS Deformable Dose Accumulation Algorithm Using 3D Gel Dosimetry
1. Introduction

dMORFEUS is the deformable dose accumulation module in MORFEUS. To accumulate dose in an organ such as the liver through a particular motion such as from exhale to inhale, dMORFEUS requires the primary and secondary FEMs which represent the initial and final positions of the organ, the deformation profile at each node of the FEM, and the primary and secondary dose grids. The primary dose grid, which describes the static dose distribution at the organ’s initial position, is denoted as $D_i$; and the secondary dose grid, which describes the static dose distribution at the organ’s final position, is denoted as $D_f$. The organ deformation from the initial position to the final position is then divided into $N$ discrete intermediate phases. The dose distribution at each intermediate phase is obtained by a combined linear interpolation from both $D_i$ and $D_f$. The accumulated dose at a point $(x, y, z)$ in the primary model as the deformation is occurring is described by the following equation:

\[
D(x, y, z) = \sum_{\phi=0}^{N} \left[ \left[ D_i(x + \frac{\phi}{N} \Delta x, y + \frac{\phi}{N} \Delta y, z + \frac{\phi}{N} \Delta z)(\frac{N-\phi}{N}) \right] + \right. \\
\left. \left[ D_f(x + \frac{N-\phi}{N} \Delta x, y + \frac{N-\phi}{N} \Delta y, z + \frac{N-\phi}{N} \Delta z)(\frac{\phi}{N}) \right] \right]
\]

EQN 4.1

in which $\phi$ is the index of the motion phase ($\phi = 0$ refers to the initial position; $\phi = 1$ to $N-1$ refer to the intermediate phases; and $\phi = N$ refers to the final position), $(\Delta x, \Delta y, \Delta z)$ is the deformation vector that describes the displacement of the initial point $(x, y, z)$ to its final position\textsuperscript{48,52}.

Although the dMORFEUS deformable dose accumulation algorithm has a sound theoretical base, it has not yet been empirically validated. Therefore, the experimental validation of the
dMORFEUS dose accumulation is the focus of this chapter. By using the dose measured with deformable gel dosimeters as the reference, the dMORFEUS dose accumulation result can be compared and evaluated.

2. Deformation Study 1

2.1 Material and Methods

2.1.a Experiment Procedure

Gel Fabrication:

Six deformable gel dosimeters were manufactured in the same batch according to the procedure described in Chapter II, Section 2.2.a. Three gels, denoted DS1-1 (Deformation Study 1), DS1-2, and DS1-3, were used to generate the R2-dose calibration curve, and thus were treated without any applied deformation. The other three gels, denoted DS1-4, DS1-5, and DS1-6, were used to measure dose under the condition of deformation. All six gels were irradiated with the same conformal plan consisting of 12 beams with a prescription of 400 cGy to a virtual GTV at the gel centre. The treatment design for all six gels is summarized in Table 4.1.

Each gel had three external markers to aid positioning on the CT simulator, the treatment couch, and the MR simulator. To assess the accuracy of deformation modeling in rMORFEUS, cylindrical gold seeds with 1 mm diameter and approximately 3mm in length were implanted in DS1-4 to DS1-6 after the gels became solidified as fiducial markers. A total of six gold seeds were used: one implanted at the centre of DS1-4 and DS1-6, and four implanted in DS1-5.
<table>
<thead>
<tr>
<th>Gel</th>
<th>DS1-1</th>
<th>DS1-2</th>
<th>DS1-3</th>
<th>DS1-4</th>
<th>DS-5</th>
<th>DS-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Calibration</td>
<td>Measure dose with applied deformation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of Deformation Applied</td>
<td>No deformation applied</td>
<td>No deformation applied</td>
<td>No deformation applied</td>
<td>2 cm</td>
<td>1.5 cm</td>
<td>1 cm</td>
</tr>
<tr>
<td>Treatment Plan</td>
<td>12-field conformal plan delivering 4 Gy to the centre of the gels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Gold Seeds Implanted</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.1. Treatment Design for the Six Gel Dosimeters in Deformation Study 1

Pre-Treatment CT Simulation:

Since the gel dosimeters were fabricated in the same batch and were moulded in the same type of paper cups, the CT simulation of one dosimeter was deemed appropriate to represent all six dosimeters. DS1-6, which had been randomly chosen, was imaged in the sample chamber of the actuation device to mimic the way the gels were to be treated. The treatment plan was then generated on the CT images of DS1-6.

Treatment:

The treatment took place 12 hours after the CT simulation. DS1-1, DS1-2, and DS1-3 were positioned by aligning the external markers with the laser beams. The positioning process was found to be difficult. The markers adhered to the plastic wrap, which could slip on the gel surface, and the marker locations had changed from the time of CT simulation to the time of treatment. A CBCT image was then taken to perform an online rigid registration with the planning image. Gel positions were then further adjusted by couch shift. Next, the gels were treated inside the sample chamber of the actuation device with the motor turned off.
The treatment process for DS1-4, DS1-5, and DS1-6 was similar with a couple of differences. First, after initial laser beam positioning, the gels were placed in the sample chamber of the actuation device with the motor turned on, delivering the desired deformation to each dosimeter at the frequency of 15-18 rpm, which corresponds to the frequency range of natural breathing. Second, instead of a regular CBCT, a 4D CBCT was done to capture the gel motion. The set of CBCT images representing the gels at the undeformed state were extracted and used to perform the online rigid registration with the planning CT image. The gels were then treated with the motor continuing to apply the deformation.

**MR Imaging:**

MR imaging was performed 7 hours after treatment. The imaging setup and protocol were the same as the ones employed in the reproducibility study, described in Chapter II, Section 2.2.a. Since this study was actually carried out before the reproducibility study, the same imaging parameters were used until the noise issue manifested more strongly in the reproducibility study.

**2.1.b R2-Dose Calibration**

The R2 maps of the six gel dosimeters were generated following the same procedure in the reproducibility study, described in Chapter II, Section 2.2.b. The R2 maps were then imported into Pinnacle and aligned with the planning image, which was the CT image of DS1-6, to compensate for positioning errors on the MR simulator.

To generate the R2-dose calibration curve, thirteen ROIs were selected inside regions of relatively uniform dose distribution on the planning dose grid. The average ROI volume was
37 mm$^3$ with small fluctuations. The minimum, maximum, mean, and the standard deviation of the dose values in each ROI were calculated. The same set of ROIs was applied to the R2 images of each calibration gel. Again, the minimum, maximum, mean, and standard deviation of the R2 values in each ROI were calculated (see Figure 4.1 below).

The planned dose grid with isodose lines displayed

![The planned dose grid with isodose lines displayed](image)

Figure 4.1. An Example of an ROI Selected on the Planned Dose Grid and the R2 Maps of the Three Calibration Gels in Deformation Study 1.

The dose and R2 values in this ROI generated one point on the R2-dose calibration curve for each calibration gel.
The dose and R2 values in each ROI generated one point on the R2-dose calibration curve for each calibration gel. The mathematical relationship between R2 and dose was subsequently obtained by fitting the data points to a linear function. By applying the R2-dose relationship to the R2 maps of the other three gels, namely DS1-4, DS1-5, and DS1-6, the dose measurements under the condition of deformation could be acquired.

2.1.c Deformation Modeling and Characterization in rMORFEUS

Accurate dose accumulation in dMORFEUS requires a quantitative characterization of the motion that the gel dosimeters, namely DS1-4 to DS1-6, had experienced during irradiation.

The first step was to sort the 4D CBCT images of each of these three dosimeters acquired in the treatment room into a series of 3D images corresponding to different phases of one motion cycle. In particular, the images of the gels at the undeformed and fully deformed states were extracted and imported into Pinnacle. The undeformed CBCT image for each gel was referred as the primary image set, whereas the fully deformed CBCT image was referred as the secondary image set. The external boundary of each gel was then delineated on the primary and secondary images, respectively. The contours were exported out of Pinnacle as binary mask files.

Next, for each gel, two surface meshes of 3.5 mm triangular elements were generated from the mask files. The mesh of the undeformed gel was the primary model, whereas the mesh of the fully deformed gel was the secondary model. In order to accurately model the compression of the piston onto the gel, rMORFEUS with contact surfaces was used to model the deformation. The contact surface technique has recently been implemented in rMORFEUS to model the motion of lungs in respiratory cycles. This technique requires a
third mesh, referred as the ‘body’ mesh, to enclose the organ mesh. A contact surface is created between the body and the organ meshes, and relative sliding motion is allowed along the contact surface. In this project, the body mesh was generated by scaling the primary mesh up by a factor of two to enclose the gel model and represent the piston that compressed the gel. An elastic modulus of 9.3 kPa, which had been measured with the tissue elastometer described in Chapter I, Section 5.1, and a Poisson’s Ratio of 0.48, were applied to the primary mesh. The deformation of the gel surface from undeformed to fully deformed state was obtained by surface projection from the primary mesh to the secondary mesh, and was set as the boundary condition on the body mesh. No explicit boundary condition was applied to the gel mesh, however it was deformed due to its contact with the body mesh. The primary model was then converted into a volumetric tetrahedral mesh, and the displacement of each node of the gel volumetric mesh was determined through finite element analysis (Abaqus v6.7, Simulink INC, Boston, MA).

The gold seeds implanted in DS1-4, DS1-5, and DS1-6 were used to assess the accuracy of the deformation analysis. The seeds were identified from the primary and secondary CBCT images of each gel to obtain the measured seed displacement. The calculated seed displacement from the FEA was then compared against the measured displacement.

2.1.d Dose Accumulation in dMORFEUS

For each of DS1-4, DS1-5, and DS1-6, the primary and secondary dose grids used in the dMORFEUS dose accumulation algorithm were produced by calculating the treatment plan on the primary and secondary CBCT images, respectively. The treatment planning CT image, which was acquired 12 hours before irradiation, was deemed not reflective of the treatment
positions of the gels, because of the non-rigidity of the gels and the positioning difficulties experienced when setting the gels up on the treatment couch. In contrast, the CBCT images were acquired immediately prior to the irradiation, and they were a better representation of the gels’ treatment positions. However, CBCT images cannot provide true gel density information, which is necessary for accurate dose calculation in Pinnacle. Fortunately, the CT images obtained in this and previous studies show that gels are tissue-equivalent and highly homogeneous. Therefore, the gel density on the CBCT images was overridden with a constant value of 1.03 g/cm$^3$; the density of the wall of the sample chamber that contained the gels, as well as the density of the piston, were overridden with a constant value of 1.08 g/cm$^3$. The remaining space on the CBCT images was air, therefore was assigned the density of 0 g/cm$^3$.

The motion of each gel was divided into six discrete steps. Since the motion was sinusoidal with respect to time, the time weightings assigned to the six intermediate steps were: 0.27, 0.12, 0.11, 0.11, 0.12, and 0.27, with a sum of 1. Based on the primary and secondary dose grids, the time step weightings, and the deformation profile generated in the rMORFEUS analysis, dose was accumulated through the motion cycle in dMORFEUS, which generated a dose distribution denoted the dMORFEUS dose for each gel.

2.1.e Comparison Between dMORFEUS Dose and Dose Measured with Gel Dosimeters

It is noticed that the measured dose maps of DS1-5 and DS1-6 have a low-dose zone inside the central high-dose regions. These seemingly low-dose zones were suspected to be artifacts on the MR images caused by the implanted gold seeds. This unexpected observation has unfortunately made the dose measurements of these two dosimeters unusable. The dose map
of DS1-4 does not display an obvious artifact, and was used to perform dose comparison with the dMORFEUS dose. Although it is not clearly visible, the seed artifact was suspected to have occurred for DS1-4 as well.

Similar to the dose comparison methods used in the reproducibility study, the dose measurement by DS1-4, which had the image resolution of $0.625 \times 0.625 \times 2 \text{ mm}^3$ as the MR images, was first down-sampled to match its corresponding dMORFEUS dose grid, the resolution of which was $2 \times 2 \times 2 \text{ mm}^3$. Then a voxel-by-voxel comparison between the measured dose and the dMORFEUS dose was performed in regions with a dose value of 200 cGy or higher according to the measured dose distribution, which was the reference dose in this case.

The procedure to compare the spatial dose distributions reflected on the gel measured dose map and the dMORFEUS dose map was also similar to the one used in the reproducibility study. The isodose surfaces of 250 cGy, 300 cGy, 350 cGy and 400 cGy were obtained from both dose maps. The distance between each pair of isodose surfaces was then computed.

2.1.f Summary of the Experiment Procedure and Data Analysis Methods

The experiment workflow and the data analysis techniques employed in deformation study 1 are summarized in the flowchart below:
2.2 Results and Discussion

2.2.a R2-Dose Calibration

The R2-dose calibration curves obtained from the three calibration gels – DS1-1, DS1-2, and DS1-3, are displayed below:
Figure 4.3. R2-Dose Calibration Curves in Deformation Study 1 Obtained from DS1-1, DS1-2, and DS1-3

The error bars reflect the standard deviation of R2 values in the ROIs. The R^2 values of 0.97, 0.97 and 0.96 for the three calibration gels respectively show that the R2-dose relationship can be satisfactorily described by a linear fit, and that the three gels had very consistent responses to the same conformal plan delivered under static conditions. The average of the three linear equations is:

\[ R2 = 1.01 \text{ Dose} + 0.86 \quad \text{EQN 4.2} \]

EQN 4.2 was then used to convert the R2 maps of the other three gels, namely DS1-4, DS1-5, and DS1-6, into dose grids.

2.2.b Deformation Modelling and Characterization in rMORFEUS

For DS1-4, DS1-5, and DS1-6, to which deformations were applied during treatment, the results of comparing the measured seed positions and the seed positions estimated by

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rMORFEUS in the LR, AP, and SI directions are displayed in the following three tables. In each table, error represents the difference between the measured seed displacement and the displacement calculated by rMORFEUS. The value of the absolute error is also displayed.

<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LR -0.24 AP 0.30 SI -0.80</td>
<td>LR 0.04 AP 0.08 SI -0.72</td>
<td>LR 0.28 AP -0.22 SI 0.08 Vector 0.36</td>
<td>0.28 0.22 0.08 0.36</td>
</tr>
</tbody>
</table>

Table 4.2. Verification of rMORFEUS Deformation Modeling for DS1-4.

The displacement of the implanted seed measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS1-4 is 2 cm.

<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LR 0.20 AP 0.15 SI -0.40</td>
<td>LR 0.04 AP 0.10 SI -0.47</td>
<td>LR -0.16 AP -0.05 SI -0.07 Vector 0.18</td>
<td>0.16 0.05 0.07 0.18</td>
</tr>
<tr>
<td>2</td>
<td>LR 0.20 AP 0.24 SI -0.40</td>
<td>LR 0.13 AP 0.26 SI -0.49</td>
<td>LR -0.07 AP 0.01 SI -0.09 Vector 0.11</td>
<td>0.07 0.01 0.09 0.11</td>
</tr>
<tr>
<td>3</td>
<td>LR 0.20 AP 0.33 SI -0.80</td>
<td>LR 0.10 AP 0.23 SI -0.78</td>
<td>LR -0.10 AP -0.11 SI 0.02 Vector 0.15</td>
<td>0.10 0.11 0.02 0.15</td>
</tr>
<tr>
<td>4</td>
<td>LR 0.42 AP 0.16 SI -1.20</td>
<td>LR 0.24 AP 0.23 SI -1.10</td>
<td>LR -0.18 AP 0.07 SI 0.10 Vector 0.21</td>
<td>0.18 0.07 0.10 0.21</td>
</tr>
<tr>
<td>mean</td>
<td>LR 0.25 AP 0.22 SI -0.70</td>
<td>LR 0.13 AP 0.20 SI -0.71</td>
<td>LR -0.12 AP -0.02 SI -0.01 Vector 0.16</td>
<td>0.12 0.06 0.07 0.16</td>
</tr>
<tr>
<td>SD</td>
<td>LR 0.11 AP 0.08 SI 0.38</td>
<td>LR 0.08 AP 0.07 SI 0.30</td>
<td>LR 0.05 AP 0.07 SI 0.09 Vector 0.04</td>
<td>0.05 0.04 0.04 0.04</td>
</tr>
<tr>
<td>Max</td>
<td>LR 0.42 AP 0.33 SI -0.40</td>
<td>LR 0.24 AP 0.26 SI -0.47</td>
<td>LR -0.07 AP 0.07 SI 0.10 Vector 0.21</td>
<td>0.18 0.11 0.10 0.21</td>
</tr>
<tr>
<td>Min</td>
<td>LR 0.20 AP 0.15 SI -1.20</td>
<td>LR 0.04 AP 0.10 SI -1.10</td>
<td>LR -0.18 AP -0.11 SI -0.09 Vector 0.11</td>
<td>0.07 0.01 0.02 0.11</td>
</tr>
</tbody>
</table>

Table 4.3. Verification of rMORFEUS Deformation Modeling for DS1-5.

For each of the four implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS1-5 is 1.5 cm.
<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LR 0.15 AP 0.26 SI -0.40</td>
<td>LR -0.02 AP 0.09 SI -0.47</td>
<td>LR -0.17 AP -0.17 SI -0.07 Vector 0.26</td>
<td>LR 0.17 AP 0.17 SI 0.07 Vector 0.26</td>
</tr>
</tbody>
</table>

Table 4.4. Verification of rMORFEUS Deformation Modeling for DS1-6.

The displacement of the planted seed measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS1-6 is 1 cm.

For DS1-5 and DS1-6, the absolute errors in seed displacement calculations are less than 2 mm, which was the resolution of the CBCT images and CBCT-based dose grids. However, for the seed implanted in DS1-4, which had the largest deformation of 2 cm, the absolute error is 2.8 mm in the left-right direction and 2.2 mm in the anterior-posterior direction. These slightly larger errors might be due to uncertainties in contouring the gels and/or picking the gold seeds on the CBCT images, since the seeds themselves have introduced significant artifacts on the CBCT images, especially on the seed-containing slices. Thus for DS1-4, although the errors were slightly above the ideal value of less than 2 mm, they were still deemed acceptable. Therefore, it can be asserted that the deformation modeling in rMORFEUS was accurate that the average error is in the same order or magnitude with or less than the associated image resolution.

2.2.c Seed-Induced Artifact on Measured Dose Distributions

As mentioned earlier in Section 2.1.e, the implanted gold seeds have caused very noticeable artifacts on the dose measurement maps for DS1-5 and DS1-6, as shown in the figures below:
The artifacts are likely caused by the magnetic susceptibility of the gold seeds. Due to the artifacts present in DS1-5 and DS1-6 dose maps, dose analysis was performed for DS1-4 only.

2.2.d Comparison Between dMORFEUS Dose and Dose Measured with Gel Dosimeters

The axial cross-sectional snapshots of the dMORFEUS dose, the gel dose, and the dose difference between the two are displayed below. The region over which dose comparison was performed is outlined in black on each snapshot. The result of voxel-by-voxel comparison between the dose measured with DS1-4 and the dose accumulated in dMORFEUS is shown in the histograms following the snapshots. The first histogram displays the percentage volume versus dose difference in centigray, with the bin width of 12.5 cGy; the second histogram displays the percentage volume versus percentage dose difference in percentage,
with the bin width of 6.25%. The percentage dose difference was calculated by the following equation:

\[
\% \text{ Dose Difference} = \frac{dMORFEUS \text{ Dose} - Gel \text{ Dose}}{Gel \text{ Dose}} \times 100\% \quad \text{EQN 4.3}
\]

On each histogram, the mean and standard deviation (SD) of the dose difference or percentage dose difference, as well as the percentage voxels falling in the range of mean ± 1SD, are also displayed.
dMORFEUS dose (cGy)

DS1-4 dose (cGy)

dMORFEUS – DS1-4 (cGy)
Figure 4.5. Results of the Voxel-by-Voxel Dose Level Comparison Between the Dose Accumulated in dMORFEUS and the Dose Measured by DS1-4.

The magnitude of deformation applied to DS1-4 was 2cm. (a) Axial snapshots of the dMORFEUS dose, the DS1-4 gel dose, and the difference between the dMORFEUS and the gel doses. The region in which dose comparison between dMORFEUS and gel was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and gel dose for DS1-4.
The mean dose difference and percentage dose difference are small, being 5.73 cGy and 1.73%, respectively. However, the standard deviations in dose difference and percentage dose difference are large, being 52.73 cGy and 20.51% respectively. Since the same MR imaging parameters were used, the large SDs can be attributed to the MR noise issue discussed in Chapter II, Section 3.1.d. The seed-induced artifact, although not apparently visible on the gel dose map of DS1-4, could also contribute to the big SDs. Another possible reason of the large SDs may be positioning and image alignment errors. The difficulty encountered when positioning the gels on the treatment couch and MR simulator was beyond expectation due to the non-rigidity of the gels and the change in the position of the external markers. Registration of the R2 map with the primary CBCT image in Pinnacle was also challenging, because the gel, especially DS1-4, might had been permanently deformed by the applied motion during treatment delivery. In addition, the only seed implanted in the gels (for DS1-4 and DS1-6) was not sufficient to define both translational and rotational offset between the R2 map and the primary CBCT image. Inaccurate registration could compromise the result of a voxel-by-voxel dose evaluation.

The result of comparing the positions of corresponding isodose surfaces between the gel dose grid and the dMORFEUS dose grids for DS1-4 is summarized in the following table:
<table>
<thead>
<tr>
<th>Metric</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
<th>Vector [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
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<td>-0.06</td>
<td>-0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>STD</td>
<td>0.07</td>
<td>0.11</td>
<td>0.05</td>
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</tr>
<tr>
<td>abs_Max</td>
<td>0.26</td>
<td>0.41</td>
<td>0.35</td>
<td>0.42</td>
</tr>
<tr>
<td>abs_95thP</td>
<td>0.17</td>
<td>0.25</td>
<td>0.28</td>
<td>0.35</td>
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</table>

<table>
<thead>
<tr>
<th>Metric</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
<th>Vector [cm]</th>
</tr>
</thead>
<tbody>
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<td>0.31</td>
</tr>
<tr>
<td>STD</td>
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<td>0.07</td>
<td>0.04</td>
<td>0.04</td>
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<tr>
<td>abs_Max</td>
<td>0.25</td>
<td>0.39</td>
<td>0.40</td>
<td>0.42</td>
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<tr>
<td>abs_95thP</td>
<td>0.15</td>
<td>0.19</td>
<td>0.33</td>
<td>0.36</td>
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</table>

Distance between the 250 cGy isodose surfaces

<table>
<thead>
<tr>
<th>Metric</th>
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<th>SI</th>
<th>Vector [cm]</th>
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</tr>
<tr>
<td>STD</td>
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<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>abs_Max</td>
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<tr>
<td>abs_95thP</td>
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<td>0.36</td>
<td>0.41</td>
<td>0.52</td>
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</table>

Distance between the 350 cGy isodose surfaces

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<th>Metric</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
<th>Vector [cm]</th>
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</thead>
<tbody>
<tr>
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<td>-0.09</td>
<td>0.20</td>
</tr>
<tr>
<td>STD</td>
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<td>0.09</td>
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</tr>
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<td>abs_Max</td>
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<td>0.28</td>
<td>0.24</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Distance between the 400 cGy isodose surfaces

Table 4.5. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the dMORFEUS Accumulated Dose and the Dose Measured by Gel DS1-4.

The mean and 95-percentile distances between each corresponding pair of isodose surfaces are larger than the isodose surface comparison results in the reproducibility study, shown in Chapter II, Section 3.1.c. The mean distances in the superior-inferior direction between the 250 cGy, 300 cGy and 350 cGy isodose surfaces are all approximately –2.5 mm, indicating a systematic position offset between the gel dose and the dMORFEUS dose, which was highly likely caused by positioning or registration error.

2.3 Conclusion

A number of issues associated with experiment procedure have deteriorated the usability of the results of deformation study 1. First, similar to the conclusion of the reproducibility study, the MR imaging parameters need to be modified to increase the SNR in MR images, which in turn would improve the dose measurement precision of gel dosimeters. The second issue is the seed-induced artifacts, which have made the dose measurements of two dosimeters non-usable. In the next study, seeds should be implanted in the peripheral region, outside the...
ROI in which dose analysis is performed. Lastly, the difficulty encountered in gel positioning and image registration suggests the need for multiple internal markers.

3. Deformation Study 2

3.1 Materials and Methods

3.1.a Experiment Procedure

The experiment procedure of deformation study 2 is similar to the one of deformation study 1 with several changes described below.

Gel Fabrication

In deformation study 2, a total of ten gel dosimeters were fabricated in the same batch following the procedure described in Chapter II, Section 2.2.a. The gels were divided into two groups of five. Two treatment plans, a half-block beam plan and a conformal plan, were generated to treat the two groups of gels, respectively. The purpose of adding the half-block beam plan was to assess the effect of motion on a sharp spatial dose gradient. The conformal plan was the same one used in deformation study 1.

The gels in the first group, to be treated with the half-block beam plan, are denoted as DS2-HB1 (deformation study 2-half-block beam 1), DS2-HB2, DS2-HB3, DS2-HB4, and DS2-HB5. DS2-HB1 and HB2 were the control samples. They were set, treated, and imaged in rigid HDPE jars to provide the best performance of the gels in measuring the half-block beam dose distribution. Three markers are placed on the external surface of the jars for positioning purpose. DS2-HB3 to HB5 were deformable gels. They were enclosed in plastic
wraps after solidification and treated under the condition of deformation. Similar to
deformation study 1, gold seeds were implanted in the deformable gels to evaluate the
accuracy of rMORFEUS deformation modeling. Since significant seed-induced artifacts were
observed in deformation study 1, the seeds were implanted in the peripheral region of the
gels to avoid the ROI in which dose analysis and comparison were performed. The seeds also
served as fiducial markers to register the R2 maps of the gels with their CBCT images. Since
a minimum of three points is necessary to specify both translation and rotation in space, three
seeds were implanted in each deformable gel. The treatment design for the first group of gel
dosimeters is summarized in Table 4.6 below:

<table>
<thead>
<tr>
<th>Gel</th>
<th>DS2-HB1</th>
<th>DS2-HB2</th>
<th>DS2-HB3</th>
<th>DS2-HB4</th>
<th>DS2-HB5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Control samples</td>
<td>Measure dose with applied deformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Magnitude of Deformation Applied</strong></td>
<td>No deformation applied</td>
<td>No deformation applied</td>
<td>1 cm</td>
<td>1.5 cm</td>
<td>2 cm</td>
</tr>
<tr>
<td><strong>Treatment Plan</strong></td>
<td>A two-field half-block beam plan delivering a total of 488 MU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong># of Gold Seeds Implanted</strong></td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4.6. Treatment Design for the Five Gel Dosimeters Treated with the Half-Block Beam Plan in Deformation Study 2

The gels in the second group, to be treated with the conformal plan, are denoted as
DS2-Conf1 (deformation study 2-conformal 1), DS2-Conf2, DS2-Conf3, DS2-Conf4, and
DS2-Conf5. DS2-Conf1 and Conf2 were the control samples and were marked on their
external surfaces. DS2-Conf1 and Conf2 also served as the R2-dose calibration gels.
DS2-Conf3 to Conf5 were deformable gels, each of which had three seeds implanted inside.
The treatment design for the second group of gel dosimeters is summarized in Table 4.7 below:

<table>
<thead>
<tr>
<th>Gel</th>
<th>DS2-Conf1</th>
<th>DS2-Conf2</th>
<th>DS2-Conf 3</th>
<th>DS2-Conf 4</th>
<th>DS2-Conf 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Control samples</td>
<td>Measure dose with applied deformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of Deformation Applied</td>
<td>No deformation applied</td>
<td>No deformation applied</td>
<td>1 cm</td>
<td>1.5 cm</td>
<td>2 cm</td>
</tr>
<tr>
<td>Treatment Plan</td>
<td>A 12-beam conformal plan delivering a total of 495 MU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Gold Seeds Implanted</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4.7. Treatment Design for the Five Gel Dosimeters Treated with the Conformal Beam Plan in Deformation Study 2

Pre-Treatment CT Simulation:

Same as in deformation study 1, dose was to be computed on CBCT images in this study as well. Therefore, the pre-treatment CT simulation was omitted. The conformal plan generated in deformation study 1 was directly used to treat the second group of gels in this study; and the half-block beam plan was generated on the treatment planning CT image acquired in deformation study 1.

Treatment:

The treatment takes place 34 hours after gel fabrication. Each of the four control gels, namely DS2-HB1, DS2-HB2, DS2-Conf1, and DS2-Conf2, was set up on the treatment couch by aligning the external markers with the in-room laser beams. The markers were deliberately placed in a way that after laser-beam alignment, the isocentre of the linear accelerator would
be approximately at the centre of the jar. Then a regular 3D static CBCT image was acquired to further ensure that the isocentre was at or near the centre of the jar.

The six deformable gels were first placed in the sample chamber of the actuation device. They were then positioned using the laser beams to set the isocentre approximately at the centre of the gels. Positioning accuracy was not so important here, because the CBCT images acquired afterward would serve as the planning images on which dose would be computed, and to which the MR images would be registered. The motor was then turned on to deliver the desired compression to each gel at the frequency of 15-18 rpm and a 4D CBCT imaging was performed to capture the motion. The image reflecting each gel’s undeformed state was extracted. If the isocentre was too far away from the gel centre, the gel position was adjusted by couch shift.

**MR Imaging:**

The gel dosimeters were imaged 24 hours after the treatment. The four control gel dosimeters were set up by aligning their external markers with the laser beams on the MR simulator. The gels were positioned to ensure that they were in the same orientation as when they were treated and that they were placed in the centre of the head coil, where the static magnetic field and the excitation pulse are most homogeneous.

Since it has been noticed that the noise in MR images downgraded the dose measurement precision in previous studies, the imaging parameters were adjusted to increase the signal-to-noise ratio (SNR) of the images:
TE: 3.2, 61.8, 120.4, 237.7, and 472.2 ms
TR: 6000 ms
NEX: 10
K-space: $2 \times 2 \times 2$ mm$^3$ resolution, spiral trajectory consisting of six 1900 interleaves
FOV: $160 \times 160$ mm$^2$
Total Imaging Time: 28 to 29 min

The distribution of the echo times was modified to better correspond to the range of T2 values of the irradiated gels to improve T2 estimation accuracy. In previous studies, the last echo time was 320 ms, while the T2 could reach 500 ms in the low-dose regions. The echo at 472.2 ms was added to reflect the long T2s in the gel. TR was also increased from 5000 ms to 6000 ms to give the proton spins more time to recover along the longitudinal axis. The number of averages, NEX, was increased significantly from 4 to 10, to improve the SNR in the MR image. The in-plane k-space pixel size was increased from $1.5 \times 1.5$ mm$^2$ to $2 \times 2$ mm$^2$, since larger pixels also increase SNR$^{30}$. The abovementioned modifications in imaging parameters have increased the SNR in the MR images to more than 200, comparing with the SNR of 110 in previous studies.

3.1.b Dose Grid Generation

Because the conformal treatment plan used in deformation study 2 was directly copied from the plan used in deformation study 1, gel-specific dose grids needed to be generated from the CBCT images of each gel. To do so, the gel dosimeters were contoured first: the four control dosimeters were simply delineated on their static 3D CBCT images; the six deformable gels were delineated on their undeformed (primary) CBCT images and fully deformed (secondary) CBCT images, respectively. On the CBCT images of the deformable gel dosimeters, the
The density of the gels was overridden with a constant value of 1.03 g/cm³; the density of the sample chamber and the piston, were overridden with a constant value of 1.08 g/cm³. The remaining space was regarded as air, therefore was assigned a density of 0 g/cm³. The dose grids were then obtained by calculating the treatment plan on the CBCT images in Pinnacle. All dose grids in deformation study 2 have the resolution of $2 \times 2 \times 2$ mm³.

3.1.c R2-Dose Calibration

After being generated according the procedure described in Chapter II, Section 2.2.b, the R2 maps of the two calibration gels, namely DS2-Conf1 and DS2-Conf2, were imported into Pinnacle and aligned with their corresponding static CBCT images as well as their CBCT image-based dose grids calculated by Pinnacle.

To generate the R2-dose calibration curve, fourteen ROIs were selected inside regions of uniform dose distribution on the CBCT-based Pinnacle dose grid for each calibration gel. The mean ROI volume was 37 mm³ (range: 35.5 to 38 mm³). The minimum, maximum, mean, and the standard deviation of dose values in each ROI were calculated. The same set of ROIs was propagated onto the R2 images of each calibration gel. Again, the minimum, maximum, mean, and standard deviation of R2 values in each ROI were calculated.

For each calibration gel, the dose and R2 values in each ROI generated one point on the calibration curve for that gel. The mathematical relationship between R2 and dose was subsequently established by fitting the data points to a linear function. The R2-dose relationship was applied to the R2 maps of the other eight gels to convert their R2 maps into measured dose distributions.
3.1.d Deformation Modeling and Characterization in rMORFEUS

The process of modeling the deformation for the six deformable gels was very similar to the process in deformation study 1, described in Chapter III, Section 2.1.c. The primary and secondary gel contours were exported from Pinnacle as binary mask files. Next, for each gel, two surface meshes of 3.5 mm triangular elements were generated respectively from the mask files. The mesh of the undeformed gel is the primary model, whereas the mesh of the fully deformed gel is the secondary model. An elastic modulus of 6.5 kPa, which had been measured with the tissue elastometer, and a Poisson’s Ratio of 0.45, were applied to the primary mesh. The contact surface technique was utilized again to accurately model the compression applied by the piston to deform the primary model to the secondary model through finite element analysis.

The gold seeds implanted in the six deformable gels were used to assess the accuracy of the deformation analysis. Seed displacements were measured by picking the seed positions on the primary and secondary CBCT images of each gel. The seed displacement estimated by the rMORFEUS modeling was then compared against the measured displacement.

3.1.e Dose Accumulation in dMORFEUS

For each of the six deformable gels, the primary and secondary dose grids used in the dMORFEUS dose accumulation algorithm were acquired by calculating the treatment plan on the primary and secondary CBCT images, respectively. Same as in deformation study 1, the sinusoidal motion was divided into six steps with the weightings of 0.27, 0.12, 0.11, 0.11, 0.12 and 0.27. Using the primary and secondary dose grids, the time step weightings, and the deformation profile generated in the rMORFEUS deformation analysis, dMORFEUS was
able to accumulate dose through the motion cycle, generating a dose grid denoted the dMORFEUS dose for each deformable gel.

3.1.f Comparison Between Dose Measured with Control Gel Dosimeters and Static CBCT-Based Dose Grids Calculated by Pinnacle

The performance of the gel dosimeters in this study were gauged by comparing the dose measurements of the four control dosimeters with their corresponding static CBCT-based dose distributions calculated by Pinnacle. The gel dose grids were down-sampled first to match with the spatial resolution of the Pinnacle dose grids. Like in previous studies, a voxel-by-voxel comparison between the two dose grids was then carried out in regions with a dose value of 2 Gy or higher on the Pinnacle dose grid. The mean difference between the gel dose grid and the Pinnacle dose grid reflected the accuracy of the gel dosimeter in measuring radiation dose, while the standard deviation in the dose difference between the two dose grids determined the precision, or uncertainty, of the gel dosimeters.

One important purpose of the conformal treatment plan was to assess the gel dosimeters’ performance in reflecting spatial dose distribution. Therefore, for the two control gels of the conformal plan (DS2-Conf1 and DS2-Conf2), the isodose surfaces of 250 cGy, 300 cGy, 350 cGy and 400 cGy were delineated from the gel dose grid and the Pinnacle dose grid. The distance between each pair of corresponding isodose surfaces was then calculated through FEA in MORFEUS.

The half-block beam plan offered an opportunity to test the gel dosimeters’ ability in detecting a sharp dose gradient. For each of the two control gels of the half-block beam plan (DS2-HB1 and DS2-HB2), a narrow cylindrical ROI with diameter of 6 mm and length of 30
mm was created at the centre of the gel dosimeter across the dose edge, spanning 15 axial slices. The average dose in the ROI on each slice was calculated for both the gel dose grid and the Pinnacle dose grid. The dose profile across the penumbra was then plotted with respect to slice location.

The 2%/2mm test described in Chapter II, Section 2.2.e was also used to compare and evaluate the measured dose against the static Pinnacle dose for each control dosimeter.

3.1.g Comparison Between dMORFEUS Dose and Dose Measured with Deformable Gel Dosimeters.

When comparing the dose measured by the control gel dosimeters with the static CBCT-based dose grid computed in Pinnacle, the Pinnacle dose grid was regarded as the reference against which the gel dose grids were compared and evaluated, and the accuracy and precision of the gel dosimeters in dose measurement were obtained. With these parameters known, the gel dosimeters could be used as the reference to evaluate the result of dose accumulation by dMORFEUS.

The comparison between dMORFEUS dose and dose measured with the six deformable gel dosimeters also included a voxel-by-voxel dose comparison, an isodose surface comparison for the gels irradiated with the conformal plan, a penumbra dose profile analysis for the gels irradiated with the half-block beam plan, and a pass-fail test. For the pass-fail test which was used to evaluate the dMORFEUS dose accumulation result against the gel dose measurement, instead of using 2%, the precision of the gel dosimeters determined from the analysis on the control gel dose grids was set to be the allowed uncertainties in dose level in the passing criterion. For example, the two control gels treated with the conformal plan have an average
dose measurement precision of 11.7 cGy or 4.74%. Then for a deformable gel also treated with the conformal plan, let the dose value at voxel A on its dMORFEUS dose grid be \(D_{dMORF}\). If a voxel B on the gel dose grid that has a dose value of \(D_g\) such that \(|D_g - D_{dMORF}| \leq 11.7\) cGy or \(95.26\% D_g \leq D_{dMORF} \leq 104.74\% D_g\) could be found within a 2 mm neighbourhood of voxel A, then voxel A was determined to pass the test.

For DS2-Conf3 and DS2-Conf4, all analyses were carried out only in regions with a dose value of 200 cGy or above on the gel dose grid, which was the reference dose grid in this case. For DS2-Conf5, the analyses were performed in regions with a dose value of 250 cGy or above on the gel dose grid. The reason for using a smaller region of interest for DS2-Conf5 will be discussed later in Section 3.2.d. For the half-block beam plan gels, a 1 cm internal margin was applied along the gel boundary to exclude the peripheral area where oxygen might have penetrated. Dose comparison and analysis were performed in regions enclosed by this margin and have a gel dose value of at least 200 cGy.

### 3.2. Results and Discussion

#### 3.2.a R2-Dose Calibration

The R2-dose calibration curves obtained from the two calibration gels, DS2-Conf1 and DS2-Conf2 are displayed below in Figure 4.6 along with the linear trend line and the equation of the linear fit. The error bars are the standard deviation in the R2 values. The two R2-dose plots show that the two calibration gels had consistent dose responses to the same treatment plan. An \(R^2\) of 0.97 suggests a strong linear relationship between R2 and dose for both gels. The average of the two linear fits is:
This calibration equation was used to convert the R2 maps of the other eight gels into dose grids.

(a) R2-Dose Calibration Curve Generated by DS2-Conf1
$R^2 = 0.85 \text{Dose} + 0.72$

$R^2 = 0.97$

(b) R2-Dose Calibration Curve Generated by DS2-Conf2

Figure 4.6. R2-Dose Calibration Curves in Deformation Study 2 Obtained from DS2-Conf1 and DS2-Conf2

3.2.6 Deformation Modelling and Characterization in rMORFEUS

For the six deformable gels, three gold seeds were implanted to verify the accuracy of the rMORFEUS motion characterization via FEA technique. The results of comparing the measured seed positions and the seed positions estimated by rMORFEUS are displayed below in Table 4.8 to Table 4.13:
Table 4.8. Verification of rMORFEUS Deformation Modeling for DS2-HB3.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-HB3 is 1 cm.

<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>Vector</td>
</tr>
<tr>
<td>1</td>
<td>0.00  0.11 -0.70</td>
<td>0.10  0.25 -0.58</td>
<td>0.10  0.14 0.12</td>
<td>0.21</td>
</tr>
<tr>
<td>2</td>
<td>-0.02  0.12 -0.10</td>
<td>-0.09  0.14 -0.01</td>
<td>-0.07  0.02 0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>3</td>
<td>0.12  -0.03 -0.05</td>
<td>0.02  0.10 -0.03</td>
<td>-0.10  0.13 0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>mean</td>
<td>0.00  0.07 -0.28</td>
<td>0.01  0.16 -0.21</td>
<td>-0.02  0.09 0.08</td>
<td>0.16</td>
</tr>
<tr>
<td>SD</td>
<td>0.08  0.08 0.36</td>
<td>0.10  0.08 0.33</td>
<td>0.11  0.06 0.05 0.05</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>0.12  0.12 -0.05</td>
<td>0.10  0.25 -0.01</td>
<td>0.10  0.14 0.12 0.21</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>-0.02  -0.03 -0.70</td>
<td>-0.09  0.10 -0.58</td>
<td>-0.10  0.02 0.02 0.11</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.9. Verification of rMORFEUS Deformation Modeling for DS2-HB4.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-HB4 is 1.5 cm.

<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>Vector</td>
</tr>
<tr>
<td>1</td>
<td>-0.06  0.08 -1.20</td>
<td>-0.13  0.19 -1.11</td>
<td>-0.07  0.11 0.09</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.06  0.10 -0.25</td>
<td>0.03  0.21 -0.18</td>
<td>-0.03  0.11 0.07</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>-0.02  0.03 -0.10</td>
<td>-0.05  0.15 -0.18</td>
<td>-0.03  0.12 -0.11</td>
<td>0.16</td>
</tr>
<tr>
<td>mean</td>
<td>-0.01  0.07 -0.52</td>
<td>-0.05  0.18 -0.50</td>
<td>-0.04  0.11 0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>SD</td>
<td>0.06  0.04 0.60</td>
<td>0.08  0.03 0.53</td>
<td>0.02  0.00 0.11 0.01</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>0.06  0.10 -0.10</td>
<td>0.03  0.21 -0.18</td>
<td>-0.03  0.12 0.09 0.16</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>-0.06  0.03 -1.20</td>
<td>-0.13  0.15 -1.11</td>
<td>-0.07  0.11 -0.11</td>
<td>0.14</td>
</tr>
</tbody>
</table>

95
Table 4.10. Verification of rMORFEUS Deformation Modeling for DS2-HB5.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-HB5 is 2 cm.

Table 4.11. Verification of rMORFEUS Deformation Modeling for DS2-Conf3.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-Conf3 is 1 cm.
<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
</tr>
<tr>
<td>1</td>
<td>0.08 0.28 -1.20</td>
<td>0.15 0.32 -1.13</td>
<td>0.07 0.04 0.11</td>
<td>0.07 0.04 0.11</td>
</tr>
<tr>
<td>2</td>
<td>0.04 0.14 -0.20</td>
<td>0.15 0.17 -0.19</td>
<td>0.11 0.03 0.12</td>
<td>0.11 0.03 0.12</td>
</tr>
<tr>
<td>3</td>
<td>0.02 0.12 -0.10</td>
<td>-0.06 0.14 -0.22</td>
<td>-0.08 0.02 -0.12</td>
<td>0.08 0.02 0.12</td>
</tr>
<tr>
<td></td>
<td>Vector</td>
<td>Vector</td>
<td>Vector</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>0.00 0.00 0.00</td>
<td>0.00 0.00 0.00</td>
<td>0.00 0.00 0.00</td>
<td>0.00 0.00 0.00</td>
</tr>
</tbody>
</table>

Table 4.12. Verification of rMORFEUS Deformation Modeling for DS2-Conf4.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-Conf4 is 1.5 cm.

<table>
<thead>
<tr>
<th>Seed #</th>
<th>Measured Displacement [cm]</th>
<th>rMORFEUS Displacement [cm]</th>
<th>Error [cm]</th>
<th>Abs Error [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
<td>LR  AP  SI</td>
</tr>
<tr>
<td>1</td>
<td>0.02 0.13 -1.20</td>
<td>-0.02 0.17 -1.14</td>
<td>-0.04 0.04 0.08</td>
<td>0.04 0.04 0.08</td>
</tr>
<tr>
<td>2</td>
<td>-0.11 0.21 -0.20</td>
<td>0.01 0.27 -0.35</td>
<td>0.12 0.06 -0.15</td>
<td>0.12 0.06 0.20</td>
</tr>
<tr>
<td>3</td>
<td>0.21 0.15 -0.20</td>
<td>0.18 0.16 -0.21</td>
<td>-0.03 0.01 -0.01</td>
<td>0.03 0.01 0.03</td>
</tr>
<tr>
<td></td>
<td>Vector</td>
<td>Vector</td>
<td>Vector</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>0.00 0.00 0.00</td>
<td>0.00 0.00 0.00</td>
<td>0.00 0.00 0.00</td>
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Table 4.13. Verification of rMORFEUS Deformation Modeling for DS2-Conf5.

For each of the three implanted seeds, the seed displacement measured from the primary and secondary CBCT images, the displacement predicted by rMORFEUS via deformation registration technique, and the difference between the two are reported. The magnitude of deformation applied to DS2-Conf5 is 2 cm.
The absolute errors in seed displacement calculations are less than 2 mm, which was the resolution of the CBCT images and CBCT-based dose grids, for all deformable gels other than DS2-HB5, which had an absolute error of 2.2 mm in the anterior-posterior direction for seed #2, and an error of 2.0 mm in the left-right direction for seed #3. These slightly larger errors might be due to errors in contouring the gels and/or picking the gold seeds on the CBCT images, which have a significant amount of artifacts especially on the seed-containing slices. For DS2-HB5, although the errors were slightly above the ideal value of 2 mm or less, they were still deemed acceptable. Therefore, it can be asserted that the deformation modeling in rMORFEUS was accurate with an average error equal to or less than the associated image resolution.

3.2.c Comparison Between Dose Measured with Control Gel Dosimeters and Static CBCT-Based Dose Grids Calculated by Pinnacle

For the two control gels treated with the half-block beam plan, namely DS2-HB1 and DS2-HB2, sagittal snapshots of the static CBCT-based Pinnacle dose, the dose measured with the gel dosimeter, and the dose difference map between the two are displayed below. It was noticed that the dose readout in the periphery of the dosimeter was inaccurate possibly due to the magnetic field inhomogeneities caused by the jar-air and gel-jar interfaces during MR imaging. Therefore, a 1 cm wide internal margin was applied along the boundary of the dosimeter. The volume enclosed by this margin is outlined in black on each snapshot.

Following the sagittal snapshots of each gel, the result of the voxel-by-voxel comparison between the static Pinnacle dose and the gel measured dose is shown in two histograms: the first histogram displays the percentage volume versus dose difference in centigray, with the
bin width of 12.5 cGy; the second histogram displays the percentage volume versus percentage dose difference, with the bin width of 6.25%. The percentage dose difference was calculated using the following equation:

\[
\text{% Dose Difference} = \frac{\text{Pinnacle Static Dose} - \text{Control Gel Dose}}{\text{Pinnacle Static Dose}} \times 100\% \quad \text{EQN 4.5}
\]

On each histogram, the mean and standard deviation (SD) of the dose difference or percentage dose difference, as well as the percentage of voxels falling in the range of mean ± 1SD, are also displayed. The histograms only include the region enclosed by the 1 cm wide margin and with a Pinnacle dose greater than or equal to 200 cGy. The upper low dose region is excluded because the percentage dose difference is over-sensitive in this region, that a small difference in dose level, such as 10 cGy, would yield a large percentage dose difference of 50%, if the Pinnacle dose is 20 cGy at that voxel.
Figure 4.7. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Pinnacle Dose and the Dose Measured by DS2-HB1.

DS2-HB1 was irradiated under static conditions. (a) Sagittal snapshots of the static Pinnacle dose, the DS2-HB1 gel dose, and the difference between the Pinnacle and the gel doses. The 1 cm wide internal margin to exclude the gel periphery is shown in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and DS2-HB1 gel dose.
Figure 4.8. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Pinnacle Dose and the Dose Measured by DS2-HB2.

DS2-HB2 was irradiated under static conditions. (a) Sagittal snapshots of the static Pinnacle dose, the DS2-HB2 gel dose, and the difference between the Pinnacle and the gel doses. The 1 cm wide internal margin to exclude the gel periphery is shown in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and DS2-HB2 gel dose.
The snapshots of the dose difference maps show that the largest dose difference between the Pinnacle dose and the measured dose occurs at the steep dose gradient. The histograms indicate excellent agreement between Pinnacle and gel dosimeters on dose levels in regions of 200 cGy or above.

For the two control gels treated with the conformal plan, namely DS2-Conf1 and DS2-Conf2, axial snapshots of the static CBCT-based dose calculated in Pinnacle, the dose measured with the gel dosimeter, and the dose difference map between the two are displayed below. Dose comparison was performed only in the region enclosed by the 200 cGy isodose line on the Pinnacle dose grid.

Following the axial snapshots of each gel, the result of the voxel-by-voxel comparison between the gel measured dose and the static Pinnacle dose is shown in the histograms of percentage volume versus dose difference and percentage volume versus percentage dose difference. The percentage dose difference was calculated using Equation 4.5. On each histogram, the mean and standard deviation (SD) of the dose difference or percentage dose difference, as well as the percentage of voxels falling in the range of mean ± 1SD, are also displayed.
Figure 4.9. Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Pinnacle Dose and the Dose Measured by DS2-Conf1.

DS2-Conf1 was irradiated under static conditions. (a) Axial snapshots of the static Pinnacle dose, the DS2-Conf1 gel dose, and the difference between the Pinnacle and the gel doses. The Pinnacle 200 cGy isodose line inside which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and DS2-Conf1 gel dose.
Static Pinnacle Dose (cGy)  

DS2-Conf2 Dose (cGy)
Figure 4.10, Results of the Voxel-by-Voxel Dose Level Comparison Between the Static Pinnacle Dose and the Dose Measured by DS2-Conf2.

DS2-Conf2 was irradiated under static conditions. (a) Axial snapshots of the static Pinnacle dose, the DS2-Conf2 gel dose, and the difference between the Pinnacle and the gel doses. The Pinnacle 200 cGy isodose line inside which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the Pinnacle dose and DS2-Conf2 gel dose.
Both the axial snapshots of the gel dose maps and the histograms clearly indicate an increase in dose measurement precision comparing with the gel dose maps obtained in the reproducibility study. Considering the fact that except for the MR imaging parameters, the experiment procedure is identical for the three dosimeters (RS-4 to RS-6) in the reproducibility study and the two control gels of the conformal plan (DS2-Conf1 and DS2-Conf2) in this study, this increase in dose measurement precision should be attributed to the improved SNR in the MR images.

Overall, all four control gel dosimeters (DS2-HB1, DS2-HB2, DS2-Conf1 and DS2-Conf2) have demonstrated both accuracy and precision in dose measurement in regions with a dose level of 200 cGy or above.

The results of comparing the positions of corresponding isodose surfaces between the gel dose grids and the Pinnacle dose grids for DS2-Conf1 and DS2-Conf2 are summarized in Table 4.14 and 4.15:

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Table 4.14. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the Static Pinnacle Dose and the Dose Measured by Gel DS2-Conf1.
The isodose surface comparison results show that the two control gels for the conformal plan agreed very well with Pinnacle on spatial dose distribution. The absolute maximum distance between corresponding isodose surface pairs is 2.0mm, which equals the dose grid resolution.

The penumbra dose profiles obtained from the two control gel dosimeters irradiated with the half-block beam plan (DS2-HB1 and DS2-HB2) and their static Pinnacle dose grids are displayed in the Figure 4.16 below:
Figure 4.11. The Dose Edge Penumbra Profile of the Gel Dose and Pinnacle Dose for DS2-HB1 and DS2-HB2.

No motion was applied to DS2-HB1 and DS2-HB2, which were the two control gels treated with the half-block beam plan.

The penumbra dose profiles of the gel dose and Pinnacle dose agree very well with each other in general. The gels seem to overestimate the dose than Pinnacle at the highest dose gradient location at 5cm along the z-axis. This observation can be attributed to the fact that both Pinnacle and the gels have relatively large dose readout uncertainties in steep dose...
gradient region. The sharp dose falloff also makes the voxel dose values more prone to interpolation errors.

The results of the 2%/2mm test to evaluate the dose measurement performance of the four control gel dosimeters were obtained. The passing rate of voxels in the ROI for each control gel is reported in Table 4.16 below:

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<th>Criterion</th>
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<th>Conformal Plan</th>
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<td>2%/2mm</td>
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<td>DS2-Conf1 75.80%</td>
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<td></td>
<td>DS2-HB2 88.28%</td>
<td>DS2-Conf2 79.00%</td>
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Table 4.16. The 2%/2 mm Passing Rate for the Four Control Gel Dosimeters in Deformation Study 2

Higher portions of voxels for the half-block beam plan control gels have passed the 2%/2mm test than the conformal plan control gels. This could be explained by the fact that in regions where the static Pinnacle dose is greater than or equal to 2 Gy, the half-block beam plan has a much more homogeneous dose distribution than the conformal plan. Therefore the uncertainties associated with dose measurement and dose calculation across spatial dose gradients are also reduced for the gels treated with the half-block beam plan. Nevertheless, all four control gels have at least 75% voxels passing the test, confirming that gel dosimeters can provide quite accurate 3D dose measurements.

3.2.d Comparison Between dMORFEUS Dose and Dose Measured with Deformable Gel Dosimeters

For each of the three deformable gels treated with the half-block beam plan – DS2-HB3, DS2-HB4 and DS2-HB5 – a sagittal snapshot of the dMORFEUS dose, the dose measured
with the gel, and the dose difference map between the two is displayed below. A 1 cm wide internal margin was applied along the boundary of the dosimeter to exclude regions where oxygen might have infiltrated. The volume enclosed by this margin is shown on the snapshot of the dose difference map.

The results of the voxel-by-voxel comparison between dMORFEUS dose and the corresponding gel dose are shown in the histograms following the dose distribution snapshots. Again, two histograms were generated for each gel: the percentage volume versus dose difference in centigray, with the bin width of 12.5 cGy; and the percentage volume versus percentage dose difference, with the bin width of 6.25%. The percentage dose difference was calculated using the following equation:

\[
\% \text{ Dose Difference} = \left( \frac{d\text{MORFEUS Dose} - \text{Deformable Gel Dose}}{\text{Deformable Gel Dose}} \right) \times 100\% \quad \text{EQN 4.6}
\]

The mean, standard deviation (SD), and the percentage of voxels falling in the range of mean ± 1SD are shown on each histogram. The histograms only include the region enclosed by the 1 cm wide margin and with a gel dose level greater than or equal to 200 cGy.
dMORFEUS Dose (cGy)

DS2-HB3 Dose (cGy)

dMORFEUS – DS-HB3 (cGy)
Figure 4.12. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-HB3.

The magnitude of deformation applied to DS2-HB3 was 1 cm. (a) Sagittal snapshots of the dMORFEUS dose, the DS2-HB3 gel dose, and the difference between the dMORFEUS and the gel doses. The 1 cm wide internal margin to exclude the gel periphery is shown in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-HB3 gel dose.
dMORFEUS Dose (cGy)

DS2-HB4 Dose (cGy)

dMORFEUS – DS2-HB4 (cGy)
Figure 4.13. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-HB4.

The magnitude of deformation applied to DS2-HB4 was 1.5 cm. (a) Sagittal snapshots of the dMORFEUS dose, the DS2-HB4 gel dose, and the difference between the dMORFEUS and the gel doses. The 1 cm wide internal margin to exclude the gel periphery is shown in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-HB4 gel dose.
Figure 4.14. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-HB5.

The magnitude of deformation applied to DS2-HB5 was 2 cm. (a) Sagittal snapshots of the dMORFEUS dose, the DS2-HB5 gel dose, and the difference between the dMORFEUS and the gel doses. The 1 cm wide internal margin to exclude the gel periphery is shown in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-HB5 gel dose.
For each of the three deformable gels treated with the conformal plan – DS2-Conf3, DS2-Conf4 and DS2-Conf5 – an axial snapshot of the dMORFEUS dose, gel measured dose, and the dose difference map between the two is displayed below. The region inside the 200 cGy isodose surface of the gel dose grid is displayed on the dose difference map. However, for DS2-Conf5, as seen from its axial snapshot, the treatment isocentre is away from the gel, so that at least part of the high dose zone is inside the peripheral region where oxygen might have infiltrated to affect the local dose measurement accuracy. Therefore, for DS2-Conf5, instead of using the 200 cGy isodose surface, which is too close to the gel boundary, the region of interest is reduced to the volume enclosed by the 250 cGy isodose surface.

Following the axial snapshots of each gel, the result of the voxel-by-voxel comparison between dMORFEUS dose and gel dose is shown in the two histograms of percentage volume versus dose difference and percentage volume verses percentage dose difference. The percentage dose difference was calculated using Equation 4.6. On each histogram, the mean and standard deviation (SD) of the dose difference or percentage dose difference, as well as the percentage of voxels falling in the range of mean ± 1SD, are also shown.
dMORFEUS Dose (cGy)  

DS2-Conf3 Dose (cGy)  

(dMORFEUS – DS2-Conf3 (cGy))
Figure 4.15. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-Conf3.

The magnitude of deformation applied to DS2-Conf3 was 1 cm. (a) Axial snapshots of the dMORFEUS dose, the DS2-Conf3 gel dose, and the difference between the dMORFEUS and the gel doses. The gel dose 200 cGy isodose line inside which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-Conf3 gel dose.
Figure 4.16. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-Conf4.

The magnitude of deformation applied to DS2-Conf4 was 1.5 cm. (a) Axial snapshots of the dMORFEUS dose, the DS2-Conf4 gel dose, and the difference between the dMORFEUS and the gel doses. The gel dose 200 cGy isodose line inside which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-Conf4 gel dose.
dMORFEUS – DS2-Conf5 (cGy): The region enclosed by the 250 cGy isodose line is displayed.
Figure 4.17. Results of the Voxel-by-Voxel Dose Level Comparison Between the dMORFEUS Dose and the Dose Measured by DS2-Conf5.

The magnitude of deformation applied to DS2-Conf5 was 2 cm. (a) Axial snapshots of the dMORFEUS dose, the DS2-Conf5 gel dose, and the difference between the dMORFEUS and the gel doses. The gel dose 250 cGy isodose line inside which dose comparison was performed is outlined in black. (b) Histograms showing the dose difference and percentage dose difference between the dMORFEUS dose and DS2-Conf5 gel dose.
The histograms above indicate a larger discrepancy between dMORFEUS dose and dose measured with deformable gel dosimeters than between static Pinnacle dose and dose measured with control gel dosimeters. The increased discrepancy is reflected from the more widely spread out dose difference. This can be attributed to a number of uncertainties introduced mainly by the deformable nature of the gel dosimeters and the incorporation of motion during irradiation.

Similar in deformation study 1, the deformability of the gels made precise positioning on the MR simulator very difficult. When the R2 images were later aligned with the undeformed CBCT images, registration errors may also exist because of the errors in picking the seeds on both image sets due to artifacts and noises. The issue was more prominent on the CBCT images on which the seeds themselves had caused significant artefacts. In addition, since the gels are not perfectly elastic, they might be permanently deformed by the actuation device, especially when large deformations (1.5 cm and 2 cm) were applied. The permanent change in the shape of the dosimeters would definitely affect the dose distribution embedded within.

The possible sources of error in the dMORFEUS dose accumulation process include the errors in deformation modelling by rMORFEUS, and the fact that the dose was accumulated in six discrete steps instead of continuously.

Another important point is that the gel dosimeters are not perfect, and they have intrinsic dose measurement errors which can be seen from the comparison between the Pinnacle static dose and the dose measured with the control gels. These intrinsic errors also contribute to the discrepancy between dMORFEUS dose and dose measured with the deformable gels.
However, comparing with the result obtained in deformation study 1, the overall standard deviation in the dose difference between dMORFEUS and gel measurement has decreased from 52.73 cGy/20.51% to 34.3 cGy/11.71%, because of the reduced dose measurement uncertainties associated with MR image noise and the elimination of the seed-induced MR artefacts.

The mean dose difference is small for all gel dosimeters except for DS2-HB5. The discussion above could be well applied to DS2-HB5, which had the largest error in rMORFEUS motion analysis among all six deformable gels. It was also deformed by the largest magnitude of 2 cm during irradiation. The combination of the two factors may explain the unusually large mean dose difference of -20.61 cGy between dMORFEUS and the gel dose measurement by DS2-HB5.

The results of comparing the positions of corresponding isodose surfaces drawn from the gel dose grids and the dMORFEUS dose grids for DS2-Conf3, DS2-Conf4, and DS2-Conf5 are summarized in Table 4.17 to 4.19 below:
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Table 4.17. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the dMORFEUS Dose and the Dose Measured by Gel DS2-Conf3

Table 4.18. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the dMORFEUS Dose and the Dose Measured by Gel DS2-Conf4
The distance between corresponding isodose surface pairs is slightly larger than the isodose surface distance obtained when comparing the Pinnacle static dose grids with the control gel dose grids. This is expected since spatial uncertainties associated with deformable gels would be bigger than those associated with the rigid control dosimeters. The average vector distance between the four pairs of isodose surfaces is 0.09 cm, 0.12 cm, and 0.16 cm for DS2-Conf4, DS2-Conf5, and DS2-Conf6, respectively. These numbers are significantly less than the isodose surface comparison result obtained in deformation study 1 (average distance = 0.29 cm), indicating a great improvement in registration accuracy of the gel R2 maps with the CBCT images. In addition, the standard deviation in the distance between each pair of isodose surfaces is less than 0.15 cm for all gels. These results show a good agreement between dMORFEUS and gel dosimeters on the spatial dose distribution of the conformal plan delivered under the condition of deformation.

Table 4.19. Distances Between the Pair of Isodose Surfaces at 250 cGy, 300 cGy, 350 cGy and 400 cGy Drawn from the dMORFEUS Dose and the Dose Measured by Gel DS2-Conf5

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The penumbra dose profiles obtained from the three deformable gels irradiated with the half-block beam plan (DS2-HB3, DS2-HB4 and DS2-HB5) and their dMORFEUS dose grids are displayed in Figure 4.17 below:

(a) DS2-HB3 Dose Edge Penumbra Profile

(b) DS2-HB4 Dose Edge Penumbra Profile
Figure 4.18. The Dose Edge Penumbra Profile of the dMORFEUS Dose and the Gel Dose for DS2-HB3, DS2-HB4 and DS2-HB5.

The magnitudes of deformation applied to DS2-HB3, DS2-HB4 and DS2-HB5 are 1 cm, 1.5 cm, and 2 cm respectively.

The error bars in the penumbra dose profile plots are the standard deviation in dose values. One interesting observation from the plots is that the gels and dMORFEUS agree better with each other over the penumbra as the magnitude of the applied deformation increases, since larger deformation smoothed the sharp dose gradient more, and the impact of small spatial offsets on the dose difference between the two dose grids has been reduced. The penumbra plots also suggests that using gel dosimetry as the standard has verified the accuracy of dMORFEUS in estimating the influence of motions on steep dose gradients.

The pass-fail test was used to evaluate the dMORFEUS dose grids of the six deformable gels against their respective dose measurement. Instead of using the 2%/2 mm criterion which was employed in the dose analysis for the control gel dosimeters, the allowed uncertainties in dose value was set to be the dose measurement uncertainties of the control gel dosimeters.
which represent the best precision in dose measurement the dosimeters are able to achieve. The 2 mm spatial uncertainty was still included to compensate for possible errors in positioning the gel dosimeters and in the registration of the R2 maps with the CBCT images. For the half-block beam plan, the average uncertainty of the control gels is 11.2 cGy or 2.70%, whereas for the conformal plan, the average uncertainty of the control gels is 11.8 cGy or 4.74%. The uncertainties in both units of centigray and percentage were set as the passing criteria respectively, and the test results are displayed in Table 4.20 and 4.21. The tables also include a total passing rate, which is the percentage of voxels that satisfy either criterion.

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<th>Half-Block Beam Plan</th>
<th>DS2-HB3, 1 cm Def</th>
<th>DS2-HB4, 1.5 cm Def</th>
<th>DS2-HB5, 2 cm Def</th>
</tr>
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<td>SD of 2.70%/2 mm</td>
<td>78.75%</td>
<td>80.92%</td>
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<td>SD of 11.2 cGy/2 mm</td>
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<td>81.95%</td>
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<tr>
<td>Total Passing Rate</td>
<td>80.34%</td>
<td>83.35%</td>
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Table 4.20. The Passing Rates of the dMORFEUS Dose Grids of the Three Deformable Gels Irradiated with the Half-Block Beam Plan in Deformation Study 2

<table>
<thead>
<tr>
<th>Conformal Plan</th>
<th>DS2-Conf3, 1 cm Def</th>
<th>DS2-Conf4, 1.5 cm Def</th>
<th>DS2-Conf5, 2 cm Def</th>
</tr>
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<tbody>
<tr>
<td>SD of 4.74%/2 mm</td>
<td>92.11%</td>
<td>93.92%</td>
<td>89.70%</td>
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<tr>
<td>SD of 11.8 cGy/2 mm</td>
<td>90.92%</td>
<td>91.84%</td>
<td>88.60%</td>
</tr>
<tr>
<td>Total Passing Rate</td>
<td>92.82%</td>
<td>94.39%</td>
<td>90.81%</td>
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Table 4.21. The Passing Rate of the dMORFEUS Dose Grids of the Three Deformable Gels Irradiated with the Conformal Plan in Deformation Study 2

The passing rates for the six deformable gel dosimeters are all above 80%, demonstrating a good agreement between dMORFEUS dose and the dose measured by the gel dosimeters.
under the condition of deformation. The passing rates for the three gels treated with the conformal plan are approximately 10% higher than the passing rates for the gels treated with the half-block beam plan, because the passing criteria are less strict for the conformal plan gels.

Among the three gels irradiated with the conformal plan, the passing rate for DS2-Conf5 is several percent lower than the other two gels. This is consistent with the observation that the result of the voxel-by-voxel dose comparison and the isodose surface comparison for DS2-Conf5 is also slightly worse, mainly because the high dose region in DS2-Conf5 is partially in the peripheral zone of the gel where oxygen infiltration might have occurred, thus affecting the dose measurement accuracy.

3.3 Conclusion

The experiment procedure for deformation study 2 was modified to address the various issues manifested in previous studies. The resulted dose measurement performance of gel dosimeters has significantly improved. Comparison between the dose measured with the four control gels with the corresponding static Pinnacle dose has demonstrated that gel dosimeters can achieve accurate measurement in both dose levels and spatial dose distribution. For all four control dosimeters, more than 75% of the voxels in the region of interest have passed the 2%/2 mm test.

By setting the six deformable gel dosimeters as the reference, the accuracy of dMORFEUS dose accumulation that takes deformation into account has been verified. Using the dose measurement precision of the control gels as the allowable dose level uncertainty, and 2 mm as the allowable spatial uncertainty, more than 80% of the voxels on the gel dose grid in the
region of interest could find a voxel with a dose value under the allowable uncertainty within 2 mm on the corresponding dMORFEUS dose grid. This shows a good agreement between dMORFEUS dose and gel dose. In particular, for the conformal plan, which is a much more realistic radiation therapy treatment plan than the half-block beam plan, the pass rate is greater than 90%. Therefore, it can be concluded that using the best achievable dose measurement precision of gel dosimeters as the allowed discrepancies in dose levels, the dMORFEUS deformable dose accumulation algorithm has been experimentally validated using gel dosimetry.
CHAPTER 5 : Summary and Future Work
1. Thesis Summary

Radiotherapy techniques such as conformal therapy and image guidance have allowed precise delivery of high dose to the tumor while minimizing damage to the surrounding normal tissue. These advancements have made radiotherapy a promising treatment option for liver cancer. Research has shown that the liver can experience motion on the order of 1 to 3 centimetres due to respiration, which is a significant source of uncertainty in radiation delivery. Since normal hepatic tissue has a low dose tolerance above which potentially fatal radiation-induced liver disease can occur, techniques to minimize and accurately calculate the dose to the normal liver tissue should be pursued. It is therefore important to assess the effect of respiration induced motion on treatment delivery and the resultant dose distribution.

To accomplish this task, our research group has developed an FEM-based dose accumulation algorithm named dMORFEUS, which estimates the actual spatial dose distribution by combining the static dose calculated by the treatment planning system with the deformation profile of the organ of interest. Although the deformation field which is used as input to dMORFEUS has been extensively validated, the accumulation of dose has not yet been validated. The objective of this thesis work is to experimentally validate the dMORFEUS dose accumulation method by using deformable 3D gel dosimetry to measure dose under the condition of deformation.

A novel gel fabrication technique has been developed in this project to produce deformable gel dosimeters (Chapter 2). Experiments have been conducted to demonstrate that gel dosimeters could generate consistent dose measurements to the same treatment plan, so that they could serve as the reference against which dMORFEUS is compared and evaluated.
Comparison of the dose measured under static conditions with the dose calculated in Pinnacle has shown that for a treatment plan with a prescription of 400 cGy, gel dosimeters can achieve accurate dose measurement with uncertainties of less than 12 cGy.

A portable actuation device has been designed and constructed to apply breathing-mimicking motion to gel dosimeters during irradiation so that dose can be measured under the condition of deformation (Chapter 3). Testing has shown that the actuator could deliver consistent compressions with amplitude and frequency similar to those of respiration induced liver motion for at least 20 minutes.

Deformable dose accumulation studies have been carried out in this project to compare the dose accumulated by dMORFEUS with the dose measured by gel dosimeters under deformations with various amplitudes. Comparison result has demonstrated that taking the intrinsic measurement uncertainties of gel dosimeters into account, dMORFEUS agreed well with the dose measurements (Chapter 4). It can therefore be concluded that the validity of the dMORFEUS deformable dose accumulation algorithm has been experimentally confirmed.

2. Significance and Innovation

Although gel dosimetry has been used to measure 3D dose distribution for more than twenty years, limitations such as toxicity and oxygen inhibition have restricted their containment in rigid, airtight containers only. This limitation has restrained their application to static dose measurement. The novel gel fabrication technique developed in this project was able to produce deformable 3D gel dosimeters while providing the dosimeters effective oxygen protection. This is the first technique to generate dosimeters able to measure 3D dose distributions under the condition of deformation. Other studies that have used gel dosimeters
to examine the effect of breathing motion on dose deposition irradiated the dosimeters while moving them linearly as rigid bodies, failing to incorporate deformation into consideration. The gel dosimeters developed in this project can more realistically simulate the intra-fractional motions experienced by organs not limited to the liver. They can be used to validate algorithms that incorporate these motions into dose accumulation, providing more evidence-based insights on the impact of motion in radiation delivery. This information will be valuable in treatment planning, treatment outcome estimation and assessment.

In a study that compared the dMORFEUS accumulated dose taking breathing motion into account with the static dose calculated using exhale CT image of the liver, which is the current clinical practice, potentially significant changes in the minimum dose to the tumor and the maximum dose to the surrounding critical structures were observed\(^{48}\). The result of the study points out the potential shortcoming in the current clinical protocol to plan radiation therapies, and clearly indicates the importance to incorporate breathing motion in the treatment planning for liver cancers. Since dMORFEUS has been experimentally validated in this project, the clinical application of dMORFEUS can be pursued with more confidence. With its accuracy verified, dMORFEUS offers a convenient and fast method to quantitatively assess the dosimetric effects of intra- and inter-fraction motion.

### 3. Future Work

The biggest challenges encountered in the project are related to the handling of the gel dosimeters. Although plastic wrap was used to provide a flexible oxygen barrier, it was not perfectly airtight so that some oxygen infiltration still occurred, decreasing the dose sensitizing ability in gel periphery. In addition, the toxicity of the gel making materials has
made it inconvenient to work with the gels. If the deformable gel dosimetry developed in this project becomes part of a standard quality assurance procedure for deformable dose accumulation verification, improvements in the gel would be beneficial. Leuco dye-based 3D gel dosimeters would be a promising option since it is not inhibited by oxygen or any other gas in the atmosphere and has low toxicity. Although the current generation of leuco dye-based dosimeters such as PRESAGE uses rigid polyurethane as the bulk material, it may be possible to use deformable material such as gelatin and soft plastic to produce leuco dye-based dosimeters.

The maximum dose prescription to all gels used in this project was between 4 to 4.5 Gy. With the increasing popularity of hypo-fractionated radiotherapy, where a dose of 10 to 15 Gy is delivered in each fraction, it would be beneficial to increase the dose prescribed to the dosimeters to 10 to 15 Gy as well. However, this dose level may exceed the linear segment of the dose-response curve, so that a linear fit may not be appropriate to describe the dose-response relationship, and a more sophisticated fit should be investigated.

In this work, the phantom was a simple, homogeneous, cylindrical geometry. It will be an interesting application to use these gel dosimeters in anthropomorphic phantoms, which more accurately describe the human anatomy. It can be envisioned that gel dosimetry can be used to evaluate the effect of heterogeneities in deformable dose accumulation by developing a lung phantom, where the bronchial tree can be constructed from a gel dosimeter.
1. Fact Sheet - Cancer. (Jan-7-2008).


61. T.A.Aloia, R.Adam, D.Samuel, D.Azoulay, and D.Castaing. "A Decision Analysis Model Identifies the Interval of Efficacy for Transarterial Chemoembolization
