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A study of errors for 4D lung dose calculation

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To the pure soul of my dad (R.I.P.),
To my mom, and my kids.
A study of errors for 4D lung dose calculation

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

By

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List of Abbreviations

ART        Adaptive Radiation Therapy
C Gy        Centigray
CT          Computed Tomography
CTV         Clinical Target Volume
DGRT        Dose Guided Radiation Therapy
DIM         Dose Interpolation Methods
DIR         Deformable Image Registration
DME         Dose Mapping Error
DMPO        Direct Machine Parameter Optimization
DTA         Dose to Agreement
DVF         Displacement Vector Field
DVH         Dose Volume Histogram
DVM         Dose Volume Methods
EBRT        External Beam Radiotherapy
FBCT        Fan Beam Computed Tomography
GTV         Gross Tumor Volume
IGART       Image Guided Adaptive Radiation Therapy
IGRT        Image Guided Radiation Therapy
IMRT        Intensity-Modulated Radiation Therapy
ITV         Internal Target Volume
kV          Kilo-Voltage
MC          Monte Carlo
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>MU</td>
<td>Monitor Unit</td>
</tr>
<tr>
<td>MV</td>
<td>Mega-Voltage</td>
</tr>
<tr>
<td>NIST</td>
<td>National Institute of Standards and Technology</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>PRV</td>
<td>Planning Risk Volume</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiation Therapy</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>TG</td>
<td>Task Group</td>
</tr>
<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
</tr>
<tr>
<td>VCU</td>
<td>Virginia Commonwealth University</td>
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Abstract

A study of errors for 4D lung dose calculation

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To estimate the delivered dose to the patient during intra-fraction or throughout the whole treatment, it is important to determine the contribution of dose accumulated at different patient geometries to the overall dose. Dose mapping utilizes deformable image registration to map doses deposited on patient geometries at different times. Inputs to the dose mapping process are the irradiated and reference images, the displacement vector field, and a dose mapping algorithm. Thus accuracy of the mapped dose depends on the DVF and dose mapping algorithm. Dose mapping had been the subject of many research studies however, up to now there is no gold standard DIR or dose mapping algorithm. This thesis compares current dose mapping algorithms under different conditions such as choosing the planning target and dose grid size, and introduces new tool to estimate the required spatial accuracy of a DVF. 11 lung patients were used for this thesis work. IMRT plans were generated on the end of inhale breathing phases with 66 Gy as the prescription dose. Demons DVF's were generated using the Pinnacle treatment planning system DIR interface. Dtransform, Tri-linear with sub-voxel division, and Pinnacle dose mapping algorithms were compared to energy transfer with mass sub-voxel mapping. For breathing phase 50% on 11 patients, tissue density gradients were highest around the edge of the tumor compared to the CTV and the PTV edge voxels. Thus treatment plans generated with margin equal to zero on the tumor might yield the highest dose mapping error (DME). For plans generated on the tumor, there was no clinical effect of DME on the MLD, lung V20, and Esophagus volume indices. Statistically, MLD and lung V20 DME were significant. Two patients had D98 Pinnacle-DME of 4.4 and 1.2 Gy. In high dose gradient regions DVF spatial accuracy of ~ 1 mm is needed while 8 to 10 mm DVF accuracy can be tolerated before introducing any considerable dose mapping errors inside the CTV. By using ETM with mass sub-voxel mapping and adapting the reported DVF accuracy, the findings of this thesis have the potential to increase the accuracy of 4D lung planning.
1 Introduction

Lung cancer is one of the most common cancers in the world; it is the leading cause of cancer death in men and women in the United States. The American Cancer Society in the United States estimates that in 2015, 115,610 male and 105,590 female new cases of lung cancer will be diagnosed and 86,380 male and 71,660 female deaths will occur, accounting for 27% of all cancer deaths (The American Cancer Society in the United States, 2015).

Radiation has been used for many years to treat cancer with many successes, [1] [2] yet designing a successful radiation treatment plan for lung cancer remains a challenge. This is primarily because the cancer resides directly within a critical structure to human life, the lung. Tumor motion due to ventilation adds another challenge on the complexity of the treatment; motion can be up to 5 cm (Chen, et al. 2001). This motion requires definition of a planning volume that encompasses the motion or requires complex methods such as tracking or gating the tumor position. The density of the lung (~0.3 g/cc) is different from most other normal tissue densities (~1 g/cc) which presents challenges for dose calculation algorithms due to the loss of radiation equilibrium; especially when small field sizes are used for treatment [3] [4]. The patient breathing cycle is patient specific but is approximately 5 seconds from inhale to next inhale. During this time the lung volume is changing, the tumor moving, and the shape of lung and tumor are changing (or deforming) due to compression and relaxation of tissue.
While typical treatment plans are designed on one instance of patient geometry (planning geometry), the patient goes through multiple breathing cycles during radiation delivery which leads to differences in planned and delivered dose. To estimate the total dose delivered, dose contribution from different geometries can be accounted for by mapping the dose from the source geometries to a planning (reference) geometry and adding them. Estimating the delivered dose is limited by the accuracy of tissue voxel mapped from one breathing cycle to another, and by the accuracy of the dose mapping algorithm used to sum the doses.

This thesis compares different dose mapping algorithms for 4D dose calculations as functions of the dose conformity level and dose voxel resolution variables, and introduces a novel method of dose evaluation called distance to dose difference (DTD) to estimate the required spatial accuracy of a displacement vector field. In the context of lung cancer, this thesis reports required accuracy of a meaningful deformation vectors for patient cases.

This chapter gives an introduction to the dissertation. In chapter 2, dose mapping processes are introduced and dose mapping algorithms are described. In chapter 3 the thesis specific aims are described. In chapter 4, patients’ data and treatment planning design are described. Dose mapping methods are compared including consideration of dose conformity and dose grid resolution. A distance to dose difference (DTD) tool is introduced in chapter 5 to estimate the required spatial accuracy of a displacement vector field used in dose mapping. In chapter 6, a 3D-continuous distance to dose agreement (DTA) method is introduced and compared to a discrete DTA approach for DTD calculations. In chapter 7, DTD is implemented on patient cases and chapter 8 gives a summary of the thesis and a discussion of future directions.
2 Background

In this chapter the dose mapping process is described, current dose mapping algorithms are introduced, and DVF spatial accuracy is discussed by introducing the distance-to-dose difference (DTD) principle.

2.1 Dose mapping

The dose mapping process combines dose computation, deformable image registration, and dose summation based on multiple anatomic positions. In this section, dose mapping algorithms are reviewed.

2.1.1 Clinical need for dose mapping

It is well established that tissue “damage” caused by radiation depends on the integral dose delivered to the tissue. For tissues that change position as a function of time, knowledge of the integral dose requires tracking or mapping the dose between the various anatomic instances. This mapping describes changes in delivered dose due to tumor and organ-at-risk deformations as they move with respect to the radiation beams. Brock et al. [5], discussed the importance of including organ deformation in dose calculations. They calculated dose to the liver by implementing a model that incorporates rigid body motion and deformation. The author reported an average change in the prescribed dose to tumor of -0.4 Gy (range of -4.1 to 1.7 Gy). In this case, the maximum change in the prescribed
dose (1.7 Gy) results in an overdose to a nearby OAR. Similarly, if the minimum change in
the prescribed dose occurs inside the tumor, this will result in under dosing the target.

Schaly et al. [6], tracked the dose distribution delivered to tissue voxels in a prostate
case. They show that the largest dose differences in rectum, bladder, and seminal vesicles
were 29%, 2%, and 24%, respectively, after the first fraction of radiation treatment
compared to the planned dose. After 15 cumulative fractions, the largest dose differences
in rectum, bladder and seminal vesicles were 23%, 32% and 18% respectively, compared
to the planned dose. The study showed that by performing dose mapping, the physicist or
the MD can assess dose differences as compared to the planned dose. Dose mapping will
help in assuring the planned dose distribution was delivered in order to meet the desired
treatment outcome.

The need for dose mapping also depends on the type of the treatment. For lung
stereotactic body radiotherapy (SBRT) treatment, it is important to track the dose since
SBRT is delivered in fewer fractions, treats smaller target volumes, delivers at higher dose
rate, and extended fractional treatment time. Zhao [7], investigated the dosimetric effect of
intra-fraction tumor motion during gated lung SBRT delivery and found dose deviations to
95% of the PTV (D95) up to 26% for fractional dose and up to 14% for total dose.

2.1.2 Dose mapping process

Inputs to a dose mapping process include images of the irradiated geometry (Source
image), the reference geometry (Target image), a displacement vector field (DVF) which
registers common positions in these geometries, and a dose evaluation or mapping method
[Figure 1].
Deformable image registration aligns images contents taken at different times by providing a DVF that maps voxels in the target anatomy (fixed reference image) to the corresponding voxels in the source image (moving image). Once a DVF is generated it can be used to map intensity, contours, density, energy or dose.

Dose mapping uses the DVF to pull or push dose or dose related information from the irradiated source image and scores it to the target image. Figure 1 shows a simple graph of dose mapping; dose computed on an irradiated image (left) is mapped to voxels in a target image (right). The accuracy of the dose value scored back at the target depends on the accuracy of the DVF used and on the dose mapping method to estimate the dose in the irradiated geometry.

![Figure 1: On the left is the irradiated image (source); target image is on the right. Blue vectors represent DVFs that pull information from the source image to target image.](image)

### 2.1.3 Eulerian or Pull mapping method

The pull mapping method (Eulerian transformation) is one method to map the source image dose to the target image. Conceptually, the Eulerian transform pulls information
from a fixed position $r_s$ in the source image to its corresponding originating position in the target image ($r_t$), e.g. $r_t + \varphi(r_t) = r_s$, where $\varphi(r_t)$ is the displacement vector field at position $r_t$. Interpolation of the dose value at the position in the source image coordinate space is used to estimate the corresponding value as defined in the domain of the target image. That is, by mapping information from $r_t \rightarrow r_s$, $\varphi(r_t)$ enables pulling information (intensity, dose, energy and mass) from the source image ($S$) back to the target image ($T$).

### 2.1.4 Lagrangian or Push mapping method

The push mapping method utilizes a Lagrangian transformation to map source image dose points to the target. In this case, the DVF $\varphi^{-1}(r_s)$ is defined in the coordinate space of the source image ($S$), and information (intensity, dose, energy and mass) is pushed from the source image to the target image; e.g. $r_s + \varphi^{-1}(r_s) = r_t$. In the push method, coordinates $r_t$ are unlikely to land on the rectilinear coordinate space of image $T$, therefore, for point-based quantities, values on the rectilinear coordinates of image space $T$ need to be determined by interpolation or averaging of adjacent points. In this dissertation, however, the push mapping method is only used in the context of the ETM algorithm (Section 2.2.4), where energy deposition points in $S$ are mapped to voxel volumes in $T$ and masses in sub-voxels of $S$ are mapped to voxel volumes in $T$, circumventing the need for interpolation.
2.2 Introduction to dose mapping methods

2.2.1 Center of voxel approach

In the center of voxel (COV) approach, graphically shown in Figure 2, the dose value pulled by the DVF and stored at a corresponding target voxel is the dose value from the center of the source voxel, even though the point transformed by the DVF may not lie at the center of the source voxel. The COV approach uses the nearest neighbor interpolation.

Flampouri [8] used the COV method to estimate the difference between planned and delivered dose due to respiratory motion for lung treatments. The author generated 4 IMRT plans with different margins around the CTV. The authors found that the difference in CTV equivalent uniform dose (EUD) between the planed and the delivered doses was 33, 11, 1 and 0 Gy for the 4 IMRT plans used in the study.

While the COV approach might improve dose estimates compared with neglecting deformable voxel motion, it is an approximation which is sensitive to absolute voxel
positions with respect to dose gradients; e.g. dose gradients over the voxel volume are ignored [9].

2.2.2 Tri-linear interpolation method

To correct for some of the inherent limitations of the COV method, in the Tri-linear interpolation method (Figure 3), voxel centers ($r_T$) from the reference target image are mapped to the source image ($r_T + \varphi(r_T) = r_S$). The dose value at $r_S$ is interpolated via tri-linear interpolation from the 8 surrounding dose points on the rectilinear source dose matrix. The interpolated dose value is assigned to be the dose at $r_T$.

Schally [6], implemented the Tri-linear method to estimate the difference between the planned and delivered dose for a prostate treatment site due to inter-fraction motion. The author reported differences in the bladder, rectum and seminal vesicles between the planned and the delivered dose. By using 8 surrounding dose points on the rectilinear source dose grid, the tri-linear method estimates the mapped dose better than the COV method; however, it is limited by its accuracy to interpolate dose in regions where dose point values change dramatically.

Figure 3  Tri-linear dose interpolation method (adapted from Rosu (Rosu, Chetty et al. 2005)). On the left is the reference dose grid; on the right is the source dose grid. A point C in the reference dose grid moves to a new location in the source dose grid, then the dose to is estimated by the Tri-linear interpolation of the doses at the closest neighboring dose grid points a, b, c and d.
2.2.3 Octant subdivision method

To further improve dose mapping accuracy, Rosu [9], developed and implemented octant subdivision mapping method [Figure 4]. In this method, each target dose voxel is subdivided into octants sub-voxels. The dose at each sub-voxel center is computed via tri-linear interpolation method, and the dose at the target voxel center is assigned to be the average of the octant dose values.

Figure 4: adapted from [9], tri-linear dose mapping method with octant subdivision. Reference image is on the left and source image on the right. The voxel in the reference image is divided into 4 octants, the center of each octant (1, 2, 3, 4) is mapped to the source image and the dose for each point (1, 2, 3, 4) is interpolated from the known dose point around each point. The final dose is mapped back to the reference image.

Rosu et al. compared octant subdivision with Tri-linear mapping method under variable conditions including dose grid resolution (3.5, 5 and 10 mm) for 6 patients using PTV-based plans with GTV-PTV margin of 1 cm. She concluded that the dose grid resolution has no effect on mean lung dose (MLD) and EUD but does affect the NTCPs for serial organs such as the esophagus. Other organs at risk were not included in their study. Rosu et al. also reported that increased dose differences can occur in regions of high dose gradients for different mapping methods. Dose interpolation methods (DIM) do not give a reliable estimate of mapped dose in steep dose gradient regions because of voxel density
averaging, and due to the non-uniform melding of energy and mass which leads to a dose calculation error[10].

2.2.4 Energy transfer method

The inherent limitation of dose interpolation methods in dose gradient regions is due to the fact that it intrinsically violates the definition of dose.

\[
Dose = D = \frac{\varepsilon}{m} \quad \text{(ICRU. Radiation quantities and units. Report No.33)}
\]

where \(\varepsilon\) is the energy deposited in the voxel and \(m\) is the voxel mass. When a deformation occurs between \(S\) and \(T\), there is a re-arrangement of voxel contents, with voxels splitting, merging, and otherwise deviating from their original contents.

Consider two voxels in \(S\), \(D_{S1} = \frac{1}{1} = 1\) and \(D_{S2} = \frac{4}{2} = 2\) which merge into a single voxel in \(T\). A dose interpolation method will evaluate the dose as \(D_T = \frac{(D_{S1}+D_{S2})}{2} = \frac{3}{2}\), while, by definition \(D_T = \frac{(1+4)}{(1+2)} = \frac{5}{3}\), which introduces a dose error of 16.67% [10].

To overcome this limitation, Siebers and Zhong [10] implemented a Monte Carlo-based energy transfer method (ETM) for dose mapping. Standard Monte Carlo dose computations inherently compute dose via its definition; \(D = \frac{\varepsilon}{m}\), where \(\varepsilon\) is the sum of the energies deposited in the voxel and \(m\) is the voxel mass. In ETM, particle transport takes place in the source \(S\) image space as usual, however, in addition to scoring energy deposition events in the source image space, they are also scored in the target image
space at the coordinates \( r_t = r_s + \varphi^{-1}(r_s) \). At the end of the simulation, for each target voxel, the integral energy deposited is divided by the mass to get the dose.

\[
D_{rr} = \frac{\varepsilon_{rr}}{m_{rr}} \tag{1}
\]

Siebers and Zhong [10], developed and implemented ETM on a phantom case. In this thesis, specific aim one, ETM will be utilized for lung patient cases and compared with DVM and DIM methods.

2.2.5 Energy and mass congruent method (EMCM)

Conceptually, ETM will provide the proper mapped dose, however, as is evident in Equation 1, errors in the assessment of \( m_{rr} \) will directly translate into errors in dose. Zhong [11] developed EMCM to ensure consistency in energy deposited and mass in ETM. In EMCM, the mapped energy deposited is accumulated during particle transport simulation and the mapped mass is determined by using a Lagrangian mapping method to map \( n \) sub-voxels from the irradiated source geometry to the target geometry to determine the phantom mass. In order for the energy deposition to be congruent to mass mapping, the Zhong et al. point out that there should be a sufficient number of mass sampling points, and found that 64,000 sampling point is enough to ensure the energy and mass congruent.

EMCM was applied on one patient case and mass sampling for 106x86x35 dose grid with each voxel partitioned into 125,000 sub-voxels took 45 min.

2.2.6 Direct voxel tracking method

Monte Carlo dose calculations have no requirement that the patient transport geometry be on a rectilinear grid. Realizing this, Heath et al. developed a voxel warping
method (VWM) in which each voxel in the reference target anatomy is mapped to two tetrahedral volumes in the source reference space. The tetrahedral corners were mapped via Lagrangian coordinate transform, and the voxel mass was directly translated from the target to the source geometries. Using this method, the dose in the reference geometry was set as the average of the doses of the composite tetrahedral elements.

Heath et al. [12], developed, implemented and compared VWM with DIM for lung cancer treatments and found that, for realistic treatment planning scenarios no clinically significant differences were noted between DIM and VWM calculations. However, for an extreme case where (1.2 cm) target motion was not included in the plan, the target volume coverage was underestimated by up to 16% by DIM methods. The authors reported that care must be taken in choosing the dose mapping method when the organ at risk or the tumor moves into a region of high or low dose gradients; however, they did not study the effect of such error directly on organs at risk.

2.2.7 Dtransform

Heath [13] (Figure 5) also developed a volume based mapping method for mapping the energy deposited in a deformed geometry to reference geometry, which is conceptually similar to the ETM described by Siebers and Zhong [10]. While ETM requires a Monte Carlo dose calculation, Dtransform can be applied to an arbitrary dose calculation. Instead of mapping the energy depositions point by point, the fraction of the energy deposited in each deformed voxel (in the irradiated image) is mapped to each reference voxel as determined by the intersection of the warped reference voxels and the voxels of the deformed geometry.
Heath compared dtransform to VWM on a phantom case and on a patient case. She found that, when an exact transformation between the reference and target geometries was provided, the voxel and Dtransform methods produced identical results. However, when the transformation is not exact, there were discrepancies in the energy deposited on the target geometry which lead to significant differences in the dose calculated by the two methods due to registration errors.

![Figure 5: Illustration of energy mapping in two dimensions adapted from [13]. Each tetrahedron n of the reference grid is mapped to the target grid, and the fractional volume $V(j) \cap T(V(n))$ of each target voxel overlapped by the deformed tetrahedron is calculated.](image)

### 2.3 Analysis of dose mapping error

Dose mapping error (DME) is defined as the difference in dose between two dose mapping methods, assuming one of them is the gold standard. Most of the dose mapping studies report that dose mapping errors occur in steep dose gradient regions; however, the presence of high dose gradients is a sufficient but not necessary condition for DME to occur. According to the work done by Siebers et al. [10], several variables effects DME, the accuracy of the DVF, high dose and density gradient regions in the irradiated geometry.

For an artificial DVF with value of zero for all voxels, DME is zero even in the presence of high dose and tissue density gradients since no interpolation is done. Similarly,
for a DVF with a rigid shift for all voxels equal to the voxel size, DME is also zero since mapped dose is identical to the pre-mapped dose.

It is when the DVF is not accurate or has non rigid shifts DME might not be zero, depending on tissue density gradients in the irradiated geometry. This is explained with an intuitive example from Siebers et al, [10]. The example demonstrates a case where two tissue voxels in exhale geometry ($v_1$ and $v_2$) merge into one voxel in the inhale geometry ($w_1$), as shown in Figure 6.

![Figure 6: adapted from [10], voxel $v_0$ is directly mapped to voxel $w_0$, voxels $v_1$ and $v_2$ are merged into voxel $w_1$, and voxel $v_3$ is directly mapped to voxel $w_2$.](image)

In this case, a DIM method estimates the mapped dose to $w_1$ by the following equation:

$$d_{DIM}(w_1) = d_{S\rightarrow R}^{DIM}(w_1) = \frac{d(v_1) + d(v_2)}{2} = \frac{E(v_1) + E(v_2)}{M(v_1) + M(v_2)}$$

(2)

where $E(v_x)$ and $M(v_x)$ are the energy deposited and the mass in voxel $v_x$. However, the ETM computes the dose mapped to voxel $w_1$ as

$$d^T(w_1) = \frac{E(v_1) + E(v_2)}{M(v_1) + M(v_2)} = \frac{d(v_1) + d(v_2)\gamma}{1+\gamma}, \quad \gamma = \frac{M(v_2)}{M(v_1)}$$

(3)

DME can be written as the dose difference between $d_{DIM}(w_1)$ and $d^T(w_1)$

$$DME = \frac{|d^T(v_1) - d^T(v_2)|}{2(1+\gamma)}$$

(4)
From equation (4), we can conclude that no matter how big the dose gradients in the irradiated geometry, if the geometry is homogenous \((\gamma = 1)\), then \(\text{DME} = 0\). Cases where \(\gamma \neq 1\) (heterogeneous irradiated medium) and steep gradient regions lead to non-zero DME.

### 2.4 DVF accuracy requirements

No matter which dose mapping method is used, if the DVF is not perfect and the irradiated dose distribution is heterogeneous, dose mapping errors will occur. The key to reducing dose mapping uncertainty is not only dependent on the mapping method itself but to a high extent on the uncertainty in the displacement vector field used to perform dose mapping.

There are numerous DIR algorithms to calculate the DVF, however no known algorithm provides a DVF that maps tissue elements between anatomic instances without error [14-21]. In addition to developing ways to reduce DVF uncertainty, we need to ask the question: what is the required accuracy in the DVF? In other words, we might not have a perfect DVF; however we can accept a DVF with uncertainty if that uncertainty does not affect the dose.
3 Specific Aims

As described in Chapter 2, two sources of error affect dose mapping accuracy: (1) commonly used interpolation-based dose mapping method have inherent limitations when dose gradients overlap tissue density gradients and (2) erroneous displacement vector fields can map incorrect dose to the reference target image. Prior works with respect to (1) have been limited to few (<6) patient studies and with respect to (2), prior works have expended substantial efforts to reduce DVF and quantify DVF uncertainty without consideration of the DVF accuracy requirements. This dissertation addresses the clinical implications of dose mapping and its associated inaccuracies by pursuit of the following specific aims:

3.1 Specific Aim I: Dose mapping error quantification

To determine the potential clinical significance of dose-mapping error inherent in dose mapping methods for intra-fraction dose mapping for clinical lung radiation therapy patients as functions of dose matrix resolution and planning target definition.

Using ETM-EMCM as a standard, dose mapped via ETM-EMCM, dtransform, and DIM using 2-different voxel resolutions are compared for a series of 11 lung patients with 10-phase 4D CT data. In particular, two dose mapping variables are investigated, (1) the dose matrix resolution used for the primary dose calculation, testing the hypothesis that as the voxel size decreases, the DME will decrease and (2) the conformity of the dose with
respect to tissue density gradient regions, testing the hypothesis that DME will be greatest where tissue gradients and dose gradients overlap.

### 3.2 Specific Aim II: Distance-to-dose difference (DTD) tool

\[\text{To develop and describe a distance-to-dose difference tool which quantifies the maximum permitted DVF error at each voxel location that will ensure that the dose mapping error introduced is less than a pre-specified clinically relevant tolerance.}\]

The DTD tool is initially developed based using a standard discrete distance-to-agreement algorithm. Due to the interpolation error inherent in the discrete algorithm, a continuous distance-to-agreement algorithm is implemented for the DTD calculation (Chapter 6). Continuous and discrete DTD are compared on a phantom and patient case. The continuous DTD algorithm is applied to the lung patient cases to quantify DVF accuracy requirements for those patients (Chapter 7).
4 Dose mapping algorithms comparison

As discussed in Chapter 2, dose mapping accuracy depends on the DVF used to map the dose and on the dose mapping algorithm used to transfer the dose. This chapter addresses the later. The various dose mapping algorithms described in Section 2.2 can be classified as being point based (COV and DIM methods) or volume based (ETM, VWM, dtransform) algorithms. One goal of this dissertation is to study the potential clinical effect of using point based versus volume based dose mapping algorithms on the accumulated 4D dose for lung treatment site. This chapter tackles this thesis aim by implementing ETM with congruent mass mapping and comparing these results with the interpolation-based mapping algorithm included in the Pinnacle^3 treatment planning system, tri-linear interpolation with sub-voxel division and dtransform (volume based) on 11 lung cancer patients, each with a 10 phase CT.

The first part of the chapter discusses patient data, tumor motion extent, and treatment planning design. The implementation of tri-linear interpolation with subvoxel implementation is described in the second part. The third part investigates target volume characteristics which should highlight differences between the point-based and volume-based dose calculation algorithms. The fourth part tests the hypothesis that DIM and EMCM algorithms converge to similar results when a dose grid size of 2×2×2 \( mm^3 \) is used for dose calculation on the planning phase.
4.1 Patients and plans

4.1.1 Patient data

The patient data for this thesis has been collected from Project 4 of the VCU Program Project Grant (PPG) [NIH-P01-CA116602] and one patient data was obtained from the MD Anderson Cancer Center in Houston, Texas. The imaging data was obtained in accordance with approval of Institutional Review Board (IRB) protocol. The study examines 11 lung cancer patients. Although each patient has several 4DCT data sets, only one 4DCT image comprising 10 images each acquired to capture the full breathing cycle in 10 phases (phase 0% to 90%) was necessary for this thesis. For each patient, tumor motion was characterized by the motion of the tumor center-of-mass between breathing phases. The extent of tumor motion in each of the superior-inferior (S.I), anterior-posterior (AP) and lateral directions is shown in Table 1.

Table 1: The extent of patient tumor motion in left anterior (LAT), anterior posterior (AP), and superior inferior (SI) directions in cm for the 11 patients used in this study.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>LAT</th>
<th>AP</th>
<th>SI</th>
<th>3D motion vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.05</td>
<td>0.15</td>
<td>0.23</td>
<td>0.28</td>
</tr>
<tr>
<td>101</td>
<td>0.25</td>
<td>0.32</td>
<td>0.56</td>
<td>0.69</td>
</tr>
<tr>
<td>102</td>
<td>0.28</td>
<td>0.21</td>
<td>0.17</td>
<td>0.39</td>
</tr>
<tr>
<td>103</td>
<td>0.07</td>
<td>0.08</td>
<td>0.57</td>
<td>0.58</td>
</tr>
<tr>
<td>104</td>
<td>0.41</td>
<td>0.3</td>
<td>0.41</td>
<td>0.65</td>
</tr>
<tr>
<td>105</td>
<td>0.19</td>
<td>0.16</td>
<td>0.43</td>
<td>0.49</td>
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<tr>
<td>106</td>
<td>0.13</td>
<td>0.21</td>
<td>0.22</td>
<td>0.33</td>
</tr>
<tr>
<td>107</td>
<td>0.08</td>
<td>0.24</td>
<td>0.31</td>
<td>0.40</td>
</tr>
<tr>
<td>110</td>
<td>0.15</td>
<td>0.44</td>
<td>0.61</td>
<td>0.77</td>
</tr>
<tr>
<td>114</td>
<td>0.16</td>
<td>0.36</td>
<td>0.86</td>
<td>0.95</td>
</tr>
<tr>
<td>MD Anderson 38</td>
<td>0.06</td>
<td>0.26</td>
<td>2.4</td>
<td>2.41</td>
</tr>
</tbody>
</table>
4.1.2 Planning

Treatment planning requires a set of contours for specification of target tissues to be treated and normal tissues to be avoided by the radiation. For each patient, gross tumor volumes (GTVs) were contoured on each phase of a 10 phase image set by a single physician. A clinical target volume (CTV) on each breathing phase was created by adding an isotropic-8 mm margin to each GTV. The internal target volume (ITV) was produced by the union of per-phase CTVs. The PTV was created on breathing phase 0% (the planning phase) by adding an isotropic 5 mm margin to the ITV, unless otherwise specified. Spinal cord and esophagus contours on breathing phase 0% were expanded by 5 mm each to obtain organ at risk volumes (PRVs). The phase 0% total lung volume was defined as the sum of the right and left lung minus the CTV volume. A normal tissue structure was created on the planning phase by expanding the CTV by 4 cm and avoiding the interior of CTV expanded by 1 cm. These margins constitute the default margin setting for this study and conform to standard clinical practice. Zero margin plans (directly on the tumor) were also generated to permit determination of dependencies on dose conformity.

IMRT planning on phase 0% was performed with the Pinnacle Treatment Planning System (Philips Medical Systems research version 9.100) using direct machine parameter optimization (DMPO). In general, six to nine 6-MV coplanar non-opposed photon beams were chosen with angles depending on the tumor location. The prescribed dose was 66 Gy to 98% of the PTV volume [RTOG protocol 98-03]. The following constraints were applied on all the patient plans for this thesis. The lung volume receiving 20 Gy or more (V20) was not to exceed 30%. The heart volume receiving 40 Gy or more (V40) should not exceed 50%. No more than 55 Gy (V55) to 30% of the esophagus PRV. The maximal dose (D1)
to the spinal cord PRV should not exceed 45 Gy. The maximum dose to the normal tissue structure should not reach the prescribed dose 66 Gy. The maximum dose received by the PTV should be limited to 74 Gy. Table 2 lists the planning objectives for the PTV, spinal cord PRV, normal lung, esophagus PRV, heart and normal tissue ring used to generate the plans.

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>Type</th>
<th>Dose (Gy)</th>
<th>Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV</td>
<td>Minimum DVH</td>
<td>66</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Maximum dose</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Spinal cord PRV</td>
<td>Maximum dose</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Normal lung</td>
<td>Maximum DVH</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Maximum dose</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Esophagus PRV</td>
<td>Maximum DVH</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Maximum dose</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Heart</td>
<td>Maximum DVH</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Maximum dose</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Normal tissue</td>
<td>Maximum dose</td>
<td>66</td>
<td>-</td>
</tr>
</tbody>
</table>

The displacement vector fields used to deform the dose (using DIM and Dtransform) from all the breathing phases to the planning treatment plan were generated in Pinnacle using the Demons algorithm with the end of inhale phase as the fixed image and phase 10-90% as the moving images.

### 4.2 Dose mapping implementation

In this section, I discuss the inputs to each dose mapping algorithm such as the source dose computation algorithm and the DVF’s used. A description of the implementation of each dose mapping algorithm will also be given.
4.2.1 Inputs

Table 3 lists the inputs used for ETM, Dtransform, Tri-linear sub-voxeling, and Pinnacle dose mapping algorithms. Figure 7 shows the flow diagram of the dose mapping algorithms comparison.

Table 3: Inputs used to each dose mapping algorithm. N is the number of irradiated (source) breathing phases from 10% to 90%. No mapping occurs from target breathing phase 0% to 0%.

<table>
<thead>
<tr>
<th>Dose mapping algorithm</th>
<th>Source dosephase N%</th>
<th>Energyphase N%</th>
<th>Mass</th>
<th>DVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMCM</td>
<td></td>
<td>Transported on source by MC</td>
<td>Deformed source mass</td>
<td>Pseudo-inverse phase N% to 0%</td>
</tr>
<tr>
<td>Dtransform</td>
<td>MC</td>
<td></td>
<td>Source and target</td>
<td>phase 0% to N%</td>
</tr>
<tr>
<td>Tri-linear n=1</td>
<td>MC</td>
<td></td>
<td></td>
<td>phase 0% to N%</td>
</tr>
<tr>
<td>Tri-linear n=2</td>
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<td></td>
<td></td>
<td>phase 0% to N%</td>
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<tr>
<td>Tri-linear n=3</td>
<td>MC</td>
<td></td>
<td></td>
<td>phase 0% to N%</td>
</tr>
<tr>
<td>Pinnacle</td>
<td>MC</td>
<td></td>
<td></td>
<td>Phase 0% to N%</td>
</tr>
</tbody>
</table>
4.2.1.1 MC dose algorithm

MC has been used in Medical Physics for decades [22], [23], [24], [25], [26], [27]. MC dose computations are based on simulation of the paths and physics probability interactions of photon/electron particles through the accelerator head, beam modifiers, and patient geometry [28], [29], [30]. The MC method for dose computation has been shown through many research studies to calculate accurate dose distributions for clinical radiotherapy, particularly in heterogeneous patient tissues where the effects of electron transport can’t be accurately handled with conventional, deterministic dose algorithms [31], [32] [33], [30], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43].
Since the ETM mapping algorithm is based on transporting the energy on the source geometry, MC dose on each breathing phase was computed by running the ETM mapping method first. An in-house MC dose calculation system [31] which utilizes several components of the BEAMnrc/EGSnrc [26] system was used for dose calculations. Source particles for the simulation were sampled from a previously commissioned rotationally symmetric phase space generated from a BEAM simulation for the 6 MV mode of a Varian Clinac 21EX treatment machine [38]. Particle transport in patients was simulated with a modified version of DOSXYZnrc MC code [44].

The computed per phase MC dose was used as a source dose input to the rest of the DIM and Dtransform methods to be consistent and to avoid dose-calculation algorithm dose differences.

4.2.1.2 DVF’s

The DVF’s used for this thesis work were generated by the Pinnacle TPS which uses the Demons DIR algorithm to compute the DVF’s [45], [46], [45]. Demons DIR algorithm is a mono-modality algorithm that implicitly assumes a structure is represented by voxels of the same intensity in both source and target images. This makes the DVFs generated sensitive to image artifacts; this issue, however, is outside the scope of this thesis and should not affect the dose mapping algorithm comparison since the implemented dose mapping algorithms use the same DVFs.

Since the dose is mapped from breathing phases N% (N= 10, 20, 30, 40, … 90) to 0%end of inhale breathing phase, the input DVFs were the DVFs that point from breathing phase 0% to N% and were generated using the TPS Syntgra graphic user interface. The (0% to N%) DVFs were used for each of the DIM and Dtransform dose mapping algorithms.
The EMCM mapping algorithm utilizes the forward DVFs (source to target) to push the energy from the source to target image. To minimize dose mapping error due to input DVFs directions, a pseudo inverse DVF was generated using in-house algorithm [17] and used as an input for the EMCM method. The advantage of using the PIDVF is that it preserves the location of information mapped back-and-forth between image sets.

4.2.1.3 Demon’s DVF QA using contour mapping

Although the DVF’s were generated by the Pinnacle TPS, a simple QA test was performed to validate the usefulness of these DVFs using contour mapping. Figure 8 shows the flow diagram of the QA test process.
The test was conducted on all the patients. The GTV contoured by the MD on the breathing phase 0% (GTV on T0) was mapped to the planning phase N% using the PIDVFs.0ToN% (points from N %-> 0), to ensure that the PIDVF was loaded properly to the
TPS, a transcript file (terminal window) with the execution commands and details was opened during the process, also the PIDVF file resolution was different from the native Pinnacle DVF file. Figure 9 shows an example of how the process was executed from the TPS GUI. The moving image was set to phase 0% (T0) and the fixed image was set to the planning image (T1). In the contour panel, the manual GTVT0 contour was checked as the contour to be deformed.
Figure 9: Process steps in the TPS deform panel interface to map contours from the moving image (T0) to the fixed image (T1). In the panel, the GTVT0 manual contour was chosen to be mapped to the fixed phase T1.

Figure 10 shows how step 3 in Figure 8 process was executed from the TPS GUI. The moving image was set to phase 10% (T1) and the fixed image was set to the planning
image (T0). In the contour panel, the deformed GTVT0 on T1 contour generated by using the PIDVF was checked as the contour to be deformed.

Figure 10: Process steps in the TPS deform panel interface to map contours from the moving image (T1) to the fixed image (T0). In the panel, the GTVT0 (PIDVF) contour was chosen to be mapped to phase 0%.
Figure 11 shows the generated (green) and the manual GTV on phase 0% (blue) on transverse, sagittal, and coronal slices for patient P4P100 (same results for the rest of the patients are presented in Appendix II). The Dice coefficient (DC) [47] [48] [49] (Table 4) was also computed to evaluate the percentage volume overlap between the manual GTV0 and generated contours ((GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0%).

\[
\text{Dice} = \frac{2(V1 \cap V2)}{V1 + V2} \times 100 
\]

The Dice coefficient has a value of 1.0 when two contours are completely coincident and a value of 0.0 when they are entirely disparate, without any overlap. The mean DC and its standard deviation (SD) over all phases for each patient were reported in the last two rows of Table 4. The mean DC was \( \geq 92\% \) for all patients except the MD-Anderson patient, the mean DC was 82\%. The differences in the mean DC can be explained by differences in GTV volumes and locations among the patients [49], for example, the MD-Anderson patient had the smallest tumor volume \( 2.68 \text{ cm}^3 \), largest 3D-tumor motion \( 2.4 \text{ cm} \), and image artifacts existed in its image data.
Figure 11: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P100. The yellow vectors represent the DVFs (0->N%).
Table 4: Dice coefficient values for each generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% for all patients, the last two rows are the mean DC and its standard deviation over all the breathing phases for each patient.

<table>
<thead>
<tr>
<th>DC (%)</th>
<th>100</th>
<th>101</th>
<th>102</th>
<th>103</th>
<th>104</th>
<th>105</th>
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<tbody>
<tr>
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<td>91</td>
<td>96</td>
<td>97</td>
<td>95</td>
<td>95</td>
<td>97</td>
<td>85</td>
</tr>
<tr>
<td>80</td>
<td>96</td>
<td>95</td>
<td>97</td>
<td>96</td>
<td>93</td>
<td>95</td>
<td>97.5</td>
<td>96</td>
<td>96</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>90</td>
<td>96</td>
<td>97</td>
<td>97</td>
<td>96.5</td>
<td>93</td>
<td>95</td>
<td>98</td>
<td>96</td>
<td>95</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>avg</td>
<td>96</td>
<td>95</td>
<td>97</td>
<td>96</td>
<td>92</td>
<td>95</td>
<td>97</td>
<td>95</td>
<td>95</td>
<td>96.5</td>
<td>82</td>
</tr>
<tr>
<td>SD ±</td>
<td>0.3</td>
<td>0.9</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
<td>0.3</td>
<td>0.7</td>
<td>0.75</td>
<td>1</td>
<td>0.5</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Please note that the purpose of these generated contours was to test the DVFs, none of the deformed generated contours were used in 4D-DVH analysis, the MD manual contour on the planning phase was used for planning and will be used for 4D dose evaluations.

Based on the above visual comparisons and the reported DC’s of the compared contours for all patients, the (0->N%) DVFs and PIDVFs (N%->0) are suitable for use in the dose mapping study.
4.2.2 ETM algorithm implementation

ETM was implemented in our in-house integrated MC calculation system [10] with a modified DOSXYZnrc code. The modified DOSXYZnrc version was called etmDOSXYZnrc. Figure 12 shows how ETM can be run from the TPS. The ETM simulates the particle transport within the source images (breathing phases N%), but scores the energy deposition via the DVF at its mapped location in the reference image (end of inhale breathing phase). To get the input mass, CT images (target and source) were converted to material mass-density phantom using the CTCREATE program where a 55 material ramp was used in the Hounsfield unit (HU)-to-density conversion [39].

![Figure 12: screen shot of ETM MC dose calculation system integrated into the TPS via a tcl GUI.](image)

When ETM was first implemented [10] on a phantom case, the mapped dose on the reference image was computed by dividing the mapped energy by the mass of the
reference image. Since inconsistencies inherent in current CTs exist between the source and the reference image, the mass used in the mapped dose computation should be mapped from the source to the reference image to avoid dose mapping error.

For this thesis work, the energy mass congruent mapping methodology (EMCM) was used[11]. Like ETM, the mapped energy deposited was accumulated during the particle transport simulation; however, the source masses were mapped from each of the N-breathing phases to the end of inhale phase. While the energy and the mass were mapped separately for each N-phase mapping, the same DVF (N-phase to 0-phase) was used to map the energy and the mass Figure 13. To avoid any mapping uncertainty due to the direction of the DVF, a pseudo inverse DVF was used to map both the energy and the mass. Two important issues should be considered when mapping the mass; (1) any mass mapping error can directly translate to a dose mapping error, (2) since the particle energies are tracked one by one, to prevent any dose discrepancy caused by the incongruence of the two mappings, an in-house C++ program was written to divide the source mass phantom into pixel-size/n sub-voxels in X, Y and Z directions. \( n = 8 \) was used in this thesis. The mapped mass was determined by mapping (using the push method) the sub-voxels' mass from each of the breathing N phases to the 0% phase. A \( 2 \times 2 \times 2 \ mm^3 \) input dose voxel size was used for all MC dose computations and mass phantoms generation. The resulting mass sub-voxels' volume was \( 0.25 \times 0.25 \times 0.25 \ mm^3 \) which is smaller than the CT image resolution \( (0.97 \times 0.97 \times 3 \ mm^3) \). Sub-dividing the mapped mass will improve the precision of the mass mapping in the mapped dose calculations. Assuming equal volumes of irradiated and reference voxels, the final target voxel density is the average of the mapped densities.
Figure 13: flow diagram of the EMCM mapping process. The TPS input dose matrix on each breathing phase was converted to per-voxel material and mass matrix using the CTCREATE code. MC dose was computed on each i-phase. The i-phase CTCREATE phantoms were simultaneously pushed to T0 using the PID-DVF(i→0). MC energy was deposited on T0 using the PID-DVF(i→0). The final mapped dose voxel on T0 was computed by dividing the energy deposited on T0 voxel by the mapped voxel mass.

For the dose mapping algorithms comparison, I chose EMCM with mass mapping as the gold standard algorithm. This is due to the fact that EMCM directly utilizes the definition of dose (section 2.3). Using EMCM, the energy is mapped event by event in a point-wise...
fashion which makes the mapping more accurate. Also EMCM has the ability to map dose in regions of discontinuous motion. By applying mass mapping, ETM will be more accurate since both mapped energy and mass will be congruent.

4.2.3 Dtransform and Pinnacle dose mapping implementation

Dtransform [13] dose computation was run from the TPS using the in-house GUI. Inputs to Dtransform were the MC dose on each of the N breathing phases, both the N-phases and 0% phase density phantoms and the 0%-N% DVF’s [Figure 14]. The density phantoms (source and target) were converted from an EGSPHANT format (CTCREATE output) to a VMCPHANT format which is required by the Dtransform code (phantom that contains only densities without material numbers or type) using an in-house C++ program. Outputs of the Dtransform were the (Nphase to 0 phase) mapped doses. The mapped doses were accumulated on the 0% phase by an automated script and loaded back into the TPS.
Figure 14: flow diagram of the Dtransform dose mapping process. The TPS input dose matrix on each breathing phase was converted to per-voxel material and mass matrix using the CTCREATE code then was converted to VMC phantom format that didn’t contain material information. MC dose was computed on each i-phase. The T0 voxel was divided into 6 tetrahedrons, tetrahedral corners were mapped to N-phase geometry using DVF(0→N). The overlap between the transformed voxels and the N-phase voxels was computed. The mapped dose on T0 was computed by dividing the energy and mass in the overlapped voxels.

The Pinnacle dose mapping was performed within the TPS. Inputs were the MC dose on each of the N% breathing phases and the 0%-N% DVF’s Figure 15.
4.2.4 **Sub-Voxel dose mapping code implementation**

In this section, I describe the adaptation of Rosu's Tri-linear interpolation with octant sub-divisions dose mapping method to other number of sub-voxel divisions. The implemented dose mapping code takes the reference geometry dose matrix and sub-divides each voxel.
to \( n^3 \) sub-voxels. For each sub-voxel, the voxel centroid is mapped to the irradiated geometry and dose at the corresponding point in the irradiated geometry is determined by Tri-linear interpolation. For each reference voxel, the average dose by the \( n^3 \) sub-voxels is assigned to the dose for the voxel in the reference geometry.

Figure 16: flow diagram of the sub-voxel mapping code. Each reference voxel is divided to \( n^3 \) sub-voxels. Each reference sub-voxel point coordinate is computed and mapped by the DVF to locate its corresponding location in the irradiated geometry. The sub-voxel dose at the irradiated point is computed by Tri-linear interpolation. The average dose by \( n^3 \) the sub-voxels is assigned to the dose for the voxel in the reference geometry.

4.3 Determining target volume with maximum DME potential

In this section, I investigate the effect of choosing a planning target on dose mapping methods. The first part of this section determines which margin around the tumor is expected to result in large DME. In the second part, the determined margin is used to generate treatment plans on the reference phase for each patient, then 4D cumulative dose
estimates are computed using EMCM, tri-linear (with sub-voxels), Pinnacle, and Dtransform and compared.

4.3.1 Motivation

DME occurs when the DVF used for mapping the dose is not accurate, density and dose gradients exist in the irradiated geometry (section 2.3). High dose gradients are expected on the target borders where there is a sharp fall off of the dose. Density gradients on the target border depend on how the target is defined and what structures are surrounding it. If the density gradient on the GTV, CTV, and PTV borders was computed, the target that has the highest density gradient on its border would provide a good study case for potential DME analysis.

4.3.2 Method

The tumor, CTV and PTV mask files were extracted from the TPS system using a Pinnacle script. The script returns a binary mask (1 if inside the contour, 0 if outside) generated from an ROI. 'Inside' was defined as a voxel whose center is within the polygon defined by the contour on a particular slice. A mask was applied (using in-house C++ algorithm) on the generated contour files to determine the edge voxels around each contour Figure 17. The generated mask files had the same file size as the original contour files with values of 1 and 0. Values of one represented the edge voxels, whereas values of zero represented voxels everywhere else in the contour file. The tumor, CTV, and PTV edge voxels mask files were imported into the MATLAB workspace and new files that contain only the voxels with values of one were generated using the “find” indices equal to one command.
To evaluate the image gradient (a surrogate for mass gradient) on the edge voxels of each of the tumor, CTV, and PTV contours, the irradiated CT image was imported into MATLAB and its gradient was computed. The image gradient was computed in the X, Y, and Z directions using the MATLAB gradient function. The 3D image gradient magnitude was determined by computing the square root of the sum of the squares of each image gradient vector in the X, Y, and Z directions.

$$3D.\text{imageGradient} = \sqrt{G.x^2 + G.y^2 + G.z^2}$$  \hspace{1cm} (6)
Once the 3D image gradient was computed, the image gradient on each of the tumor, CTV, and PTV edge voxels was found by returning the values of the 3D image gradient at the specified edge voxel indices (tumor, CTV, and PTV voxels with values of one). Histograms of the generated files were then computed. From the histograms, complementary cumulative distribution functions (CCDF which is 1-CDF) of the frequency of the 3D edge voxel image gradients were generated and plotted. Since DME is proportional to the mass gradient $\gamma$, the CCDF curve, which has the highest density gradient, will determine the planning target that might result in high DME.

### 4.3.2.1 Findings

PTV, CTV, and tumor CCDF’s versus breathing phase 50% CT image gradients on the edge voxels were plotted for each of the 11 lung patients [Appendix II]. To present the results for all the 11 patients, the 3D image gradients on the edge voxels were sampled from each patient CCDF curve at the 50% CCDF values [Figure 18]. Please note that graphs were only generated for breathing phase 50% (end of exhalation) since this phase is the opposite phase for the breathing phase 0% (end of inhalation) and is expected to have higher average lung tissue density than the rest of the breathing phases[50-52].
Figure 18: 3D magnitude of the image gradient on edge voxels of the PTV (black triangle), CTV (red square), and tumor (blue circle) on breathing phase 50% for the 11 patients.

4.3.2.2 Analysis

The above graphs show that for the various target volumes considered on the 50% CT breathing phase, the image gradient is highest on the tumor (GTV) edges (blue curve) and lowest on the edges of the PTV (black curve). For most patients, the CTV curve (red) falls between the tumor and PTV curves. Since dose distributions aim to conform to the target volume, hypothetically, plans based on the tumor (GTV) result in the highest target DME, hence are used for other studies in this dissertation to accentuate the differences.
4.3.3 **Comparison of dose-mapping algorithms for 4D GTV-based plans**

for $2 \times 2 \times 2 \ mm^3$ dose grid size

4.3.3.1 **Purpose**

To compare dose-mapping algorithms using the GTV as the planning target for 4D-dose calculations.

4.3.3.2 **Method**

For each patient, an IMRT treatment plan was generated on phase 0 % directly on the tumor. IMRT planning optimizing criteria were the same as discussed in section 4.1.2 with no PRVs created on the spinal cord or esophagus. The beams were copied to the rest of the breathing phases (10 – 90 %) and the MC dose was computed on each breathing phase using $2\times2\times2 \ mm^3$ dose grid size. The MC dose from each breathing phase was mapped back and accumulated on the reference phase using EMCM, Pinnacle, Tri-linear with Sub-voxeling n= 1, 2, and 3, and Dtransform dose mapping methods.

Comparison metrics on the reference phase were derived from dose volume histogram indices such as tumor (D98 and D50), cord (D1), esophagus (V55), mean lung dose, lung (V20), normal tissue (V66), and heart (V40). Dose and volume indices were also reported based on the differences observed in the 4D-DVHs. The cutoffs for potential clinically relevant differences were >2% volume variations for the specified parameters DVH metrics and >1 Gy differences of the spinal cord D1% >1 Gy [53]. A paired two tailed statistic test was performed on D98, D50, and MLD to determine if the difference among
the dose mapping methods was statistically significant (p-value < 0.05). Voxel by voxel total dose difference statistics were also reported to identify differences that did not show up in the DVHs.

4.3.3.3 Results and analysis

For each patient, Table 14 [Appendix IV] displays the 4D-DVHs of the accumulated dose on the reference phase. For all of the dose mapping methods for the tumor, lung, esophagus, heart, cord, and normal tissue on the left. On the right is the difference in DVH indices among the dose mapping methods with respect to EMCM: Pinnacle-EMCM (Pin), Tri-linear with number of voxels 1-EMCM (N1), Tri-linear with number of voxels 2-EMCM (N2), Tri-linear with number of voxels 3-EMCM (N3), and Dtransform-EMCM (Dtran). D98, D50, MLD, and cord D1 are reported in cGy. Percentage differences in volume indices were also reported for lung, esophagus, and normal tissue.

The lung V20Gy DME (%) and MLD DME (cGy) for all the dose mapping algorithms were not clinically significant for all patients [Figure 19 and Figure 20].

For patient P4P101, since the normal tissue volume did not get 66 Gy, V10 was chosen arbitrarily as a comparison metric. For Pinnacle, Dtransform, and Tri-linear with sub-voxels 1, 2, and 3, the normal tissue difference V10 with respect to EMCM is > 2%, which is significant. No significant differences in dose and volume indices were observed for patient P4P102 except for heart V10 (3%). These differences are attributed to the inherent difference between EMCM and the rest of the methods.
Figure 19: V20Gy DME (%) for Pinnacle (red circle), Tri-linear with nSub-voxels=3 (blue square), and Dtransform (black triangle) for the 11 patients.
Tumor D98 differences of > 1Gy were observed for all the dose mapping methods with respect to EMCM for patient P4P103 [Figure 21:P4]. [Figure 22] shows the 4D-dose y-profiles for EMCM, Dtransform and their difference. The two profiles differ by 2 Gy in the sharp dose fall off region. [Figure 23], displays the 4D-dose y-profiles for EMCM, Pinnacle and their difference, the two profiles differ also in the penumbra region by ~ -10%. Although the difference is in the penumbra region, when OARs were located in the penumbra region, the DME impacts the mapped OAR’s accuracy. The difference in EMCM and Tri-linear with \( n=3 \) 4D-dose y-profiles was minimal [Figure 24].
Figure 21: D98% DME (cGy) for Pinnacle (red circle), Tri-linear with nSub-voxels=3 (blue square), and Dtransform (black triangle) for the 11 patients.
Figure 22: P4P103 4D dose y-profiles for EMCM (green), Dtransform (green) and their difference in red. The profiles show the two methods differ by 2 Gy in the sharp dose fall off region.
Figure 23: P4P103 4D dose y-profiles for EMCM (green), Pinnacle (green) and their difference in red. The profiles show the two methods differ by ~ -10% % in the penumbra region.
There were significant differences in D98, D50 between Pinnacle and EMCM (1.2 1.14 Gy) for the MD-Anderson patient [Figure 21:P11]. Section 4.3.4 provides deep analysis on these reported results for the MD-Anderson patient. Also, difference of 3% in esophagus V10 for Pinnacle with respect to ETM was observed. There were no significant differences in cord D1, normal tissue, and heart V10.

To investigate any significant 4D dose differences that don’t show in the 4D-DVHs, DME statistics over the whole dose matrix are reported in Table 5.
Table 5. Total 4D absolute dose difference statistics (Gy) for dose mapping methods with respect to EMCM for the 11 patients.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Pinnacle-EMCM</th>
<th>Dtrans-EMCM</th>
<th>Nsub1-EMCM</th>
<th>Nsub2-EMCM</th>
<th>Nsub3-EMCM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>max</td>
<td>Avg</td>
<td>SD</td>
<td>max</td>
<td>avg</td>
</tr>
<tr>
<td>100</td>
<td>24.72</td>
<td>0.22</td>
<td>0.67</td>
<td>21.5</td>
<td>0.21</td>
</tr>
<tr>
<td>101</td>
<td>24.58</td>
<td>0.19</td>
<td>0.73</td>
<td>24.43</td>
<td>0.19</td>
</tr>
<tr>
<td>102</td>
<td>23.2</td>
<td>0.38</td>
<td>0.82</td>
<td>27.98</td>
<td>0.42</td>
</tr>
<tr>
<td>103</td>
<td>22.4</td>
<td>0.21</td>
<td>0.53</td>
<td>22.58</td>
<td>0.15</td>
</tr>
<tr>
<td>104</td>
<td>40.97</td>
<td>0.43</td>
<td>0.89</td>
<td>42.45</td>
<td>0.32</td>
</tr>
<tr>
<td>105</td>
<td>28.86</td>
<td>0.14</td>
<td>0.4</td>
<td>27.15</td>
<td>0.11</td>
</tr>
<tr>
<td>106</td>
<td>17.75</td>
<td>0.2</td>
<td>0.47</td>
<td>22.59</td>
<td>0.16</td>
</tr>
<tr>
<td>107</td>
<td>21.72</td>
<td>0.08</td>
<td>0.32</td>
<td>21.34</td>
<td>0.05</td>
</tr>
<tr>
<td>110</td>
<td>18.34</td>
<td>0.12</td>
<td>0.37</td>
<td>18.54</td>
<td>0.08</td>
</tr>
<tr>
<td>114</td>
<td>28.7</td>
<td>0.24</td>
<td>0.59</td>
<td>27.66</td>
<td>0.22</td>
</tr>
<tr>
<td>MDA</td>
<td>21.57</td>
<td>0.26</td>
<td>0.96</td>
<td>20.91</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The average absolute DME for all patients was < 1 Gy [Figure 25], which is not clinically significant; however the maximum absolute DME for all patients ranged from 18 to 41 Gy. If the maximum DME occurs in the tumor or OARs it will have an impact on the dose mapping accuracy, for example, maximum differences >20 Gy in DME sometimes in relevant normal tissue, such as airways in patient P4P101 is important for toxicity. To investigate the location of the maximum DME on patient anatomy, total 4D dose difference files were loaded back to the TPS. Figure 73-83 in Appendix V show the location of the maximum absolute DME for all patients for Pinnacle, Tri-linear with n=3, and Dtransform.
None of the maximum absolute DME points (plotted with a symbol with a 2 cm diameter) occur in the tumor for all the patients. The regular DME statistics table and the location of the maximum DME point are also included in Appendix V [Table 11, Figure 84-Figure 94].

To check if the difference in D98, D50, lung V20 and MLD is statistically significant for all dose mapping methods with respect to EMCM, a student two tailed t-test was done. P-values were reported in Table 6, a p-value < 0.05 is considered statistically significant.
P-values for the tumor D98 and D50 showed no significance, this is expected since dose in target is uniform. Lung V20 and MLD p-values were significant for all the dose mapping algorithms since dose is non-uniform.

<table>
<thead>
<tr>
<th>Pvalue</th>
<th>Pin&amp;EMCM</th>
<th>Nsub1&amp;EMCM</th>
<th>Nsub2&amp;EMCM</th>
<th>Nsub3&amp;EMCM</th>
<th>Dtrans&amp;EMCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor D98</td>
<td>0.39</td>
<td>0.24</td>
<td>0.23</td>
<td>0.23</td>
<td>0.75</td>
</tr>
<tr>
<td>Tumor D50</td>
<td>0.33</td>
<td>0.09</td>
<td>0.08</td>
<td>0.07</td>
<td>0.4</td>
</tr>
<tr>
<td>Lung V20</td>
<td>0.01</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td>MLD</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

4.3.4 Analysis of Pinnacle DME for the MD-Anderson patient:

The 4D-DVHs’ graph for the MD-Anderson showed that the difference in the 4D-DVH among Pinnacle, Dtransform, and tri-linear dose mapping algorithms was significant. This was an un-expected result since, especially considering tri-linear and Pinnacle which are both point-based dose mapping algorithms; ideally they should yield similar results. To find out the reason behind the difference between Pinnacle and Tri-linear algorithms, several tests were conducted, starting with looking at the 4D-dose distribution of the two algorithms compared to each other and to the source dose before mapping. The test was done using the two extreme phases (0% and 50%). The dose was mapped from phase 50% to phase 0% using both algorithms. Figure 26 shows the sagittal (a) and coronal (b) views of the mapped dose distribution, Tri-linear (with n =1) on the left panel and Pinnacle on the right panel.
Figure 26: sagittal (a) and coronal (b) views of the mapped dose from phase 50% to phase 0%, Tri-linear was displayed on the left panel and Pinnacle on the right.

Figure 27 compares the mapped dose (left panel) Tri-linear (a) and Pinnacle (b) to the phase 50% source dose (right panel). Please note that, the mapped dose does not cover the tumor (left panel) since it is estimated from the irradiated dose on phase 50%. On phase 50% the tumor moves outside the treatment beams (right panel).
To further analyze the differences, the same mapping test was repeated but using an in-house zero DVF. Mapping the source dose with a zero DVF is one of the basic tests that can be performed to check the accuracy of a dose mapping algorithm. With a zero DVF the output mapped dose must be identical to the source dose since there is no dose mapping done.

The DVF 0% to 50% was read into Matlab and its values were set to 0. The DVF then was exported to the patient directory and used in the mapping of the source dose (phase 50%) to the target phase (phase 0%). The Tri-linear algorithm produced a zero dose difference with the source dose however the Pinnacle algorithm did not [Figure 28].
Figure 28: coronal view of the difference between the irradiated dose on phase 50% and the mapped dose with zero DVF for Tri-linear (N=1) on the left panel and Pinnacle on the right panel.

The above results were shared with Philips Company. Philips verified that their non-commercial algorithm does not use Tri-linear dose interpolation but nearest neighbor interpolation which might explain the different results. Upon receiving a new version of Pinnacle (non-commercial) that contains a dose mapping algorithm with Tri-linear interpolation, the test was repeated with zero DVF and with the patient DVF. With the zero DVF test, Pinnacle with Tri-linear produced ~ a zero dose difference with the source dose (with in round off error) [Figure 29].
Figure 29: coronal view of the difference between the irradiated dose on phase 50% and the mapped dose with zero DVF for Tri-linear (n=1) on the left panel and Pinnacle with Tri-linear on the right panel.

With the real (patient) DVF the Pinnacle with Tri-linear interpolation algorithm showed a little different result over the Pinnacle with nearest interpolation algorithm. Figure 30 shows the accumulated Pinnacle dose before (solid line) and after (dashed line) the dose interpolation algorithm correction compared to the Tri-linear in-house code (left solid line).
For the above test case, the change in the tri-linear-based Pinnacle dose mapping algorithm was not clinically significant (mean mapped dose difference of 4.3 cGy between Pinnacle with nearest and Pinnacle with Tri-linear) to reduce the big difference that was observed between Pinnacle and the in-house Tri-linear code, the observed differences are characteristic of a process implementation difference which could result from a difference in the DVF readers used for Pinnacle and the in-house code, or from some aspect of not using translation/rotation parameters during DVFs generation, this was only observed for this patient who had large tumor motion (2.4 cm).

4.3.5 Conclusion:

In section 4.3.3, comparison of dose mapping algorithms was done on 11 lung cancer patients. Comparison metrics included 4D-DVH’s indices, voxel by voxel total dose
difference statistics, MLD, maximum DME point location on anatomy, dose profiles in the y-axis and statistical t-test.

Tumor 4D-DVH D98 was not significant for all the patients except P4P103 for all the methods, and the MD-Anderson patient (1.2 Gy for Pinnacle), for the P4P103 patient, dose profiles in the y-axis showed that DME occurs in the penumbra region. Voxel by voxel total dose difference statistics showed no clinical significance for the average DME. Although the maximum DME was clinically significant for all the patients, when loaded back to the TPS and visualized on patients anatomy, the DME was not located in the tumor or the evaluated OARs. In all patient cases there was no clinical effect on the MLD. Statistically, lung V20 and MLD showed significance for the entire dose mapping algorithms.

For the MD-Anderson patient which had considerable amount of 3D tumor motion (>10 mm ), Pinnacle dose mapping code differed significantly for D98 from all the other codes, this might be attributed to the difference in DVF Pinnacle and in-house readers.

Although I have chosen DME of 1 Gy to be the level of clinically significant difference, it remains a Radiation Oncologist’s decision whether to accept this level or not.

In conclusion, the results are patient and tumor motion specific. Please note that, as discussed in Section 0, choosing a zero margin around the tumor might yield to the highest DME as compared to generating plans on the CTV or the PTV, so the results shown above models dose mapping under non-clinical conditions designed to maximize the DME. The DME should be less when plans are generated when the effect of tumor motion is taken care by using the ITV and ITV-PTV margin.
4.4 Effect of using the PTV as a planning target on DME

4.4.1 Motivation

Section 4.3.2.1 results showed that the density gradients around the tumor were higher than the density gradients around the PTV [Figure 62-Figure 72]. For plans that are generated on the tumor, the DME might be higher than the DME when plans are generated on the PTV; however, using the tumor as a planning target is not currently an acceptable clinical treatment method due to several reasons, such as the movement of the tumor outside of the radiation beams during the treatment delivery, the probability of the presence of more disease cells around the defined tumor structure, patient setup errors, etc... To simulate a more clinically realistic scenario and to validate the results in section 4.3.2.1, in this section, we chose two patients to study the effect of using the PTV as the planning target on the DME. Similar to the rest of the patients, those patients had high density gradients around the tumor and their 4D-tumor-plans showed OARs DME.

The treatment plans’ designs were the same procedure as in Section 4.1.2: the PTV was created on breathing phase 0% (the planning phase) by adding an isotropic 5 mm margin to the ITV. Indices of comparison were the same as in section 4.3.3.2.

4.4.2 Results

Table 7 shows the 4D-DVHs of the accumulated dose on the reference phase for the tumor based plan on the left, and the PTV based plan on the right. Please note that the PTV plan was generated on the PRVs of the cord and the esophagus while the tumor plan was generated with no PRVs. To make the comparison valid between the two plans, the DVHs of the OARs with no PRVs are displayed. Visually, it can be seen that the difference
among the dose mapping methods for the heart, esophagus, lungs-tumor and normal tissue was less when the PTV plan was used. To quantify these results, tumor D98% and OAR DVH indices were reported and compared.

Table 7: 4D-DVHs of the accumulated dose on the reference phase for each patient on the left for the tumor based plan and on the right for the PTV plan.

Table 8 and Table 9 compare the DME in the DVH volume indices for the tumor, heart, lungs, normal tissue, and esophagus for the tumor based plan and PTV based plan.
for patients P4P101 and P4P102. Please note that the reported values were for the OARs that visually showed a DVH difference between the tumor based plan and PTV based plan.

In Table 8, the results for the Dtransform, tri-linear sub-voxeling (with n=1), and Pinnacle dose mapping codes show that the DME was reduced by 2.1%, 2.6%, and 2.6% for the normal tissue V10 when the PTV plan was used for planning. There was no clinical significant effect on the DME for the rest of the organs between the tumor and PTV based plan.

Table 8: P4P101 tumor and OAR volume indices for Dtransform, rcfnSub1, and Pinnacle DME for the tumor based plan and the PTV plan.

<table>
<thead>
<tr>
<th>Tumor $D_{98%}(\text{cGy})$</th>
<th>Heart $V_{10%\text{ Gy}}(%)$</th>
<th>Lungs-tumor $V_{20%\text{ Gy}}(%)$</th>
<th>Normal tissue $V_{10%\text{ Gy}}(%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4P101</td>
<td>Dtransform</td>
<td>rcfnSub1</td>
<td>Pinnacle</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>1.6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>1.6</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.19</td>
<td>0.19</td>
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<tr>
<td>2.6</td>
<td>2.6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

In Table 9, the results for the Dtransform, tri-linear sub-voxeling (with n=1), and Pinnacle dose mapping codes show that the DME for the heart V10 was reduced by 2.6%, 2.85%, and 2.65% when the PTV plan was used for planning.

Table 9: P4P102 tumor and OAR volume indices for Dtransform, rcfnSub1, and Pinnacle DME for the tumor based plan and the PTV plan.

<table>
<thead>
<tr>
<th>Tumor $D_{98%}(\text{cGy})$</th>
<th>Esophagus $V_{4%\text{ Gy}}(%)$</th>
<th>Heart $V_{10%\text{ Gy}}(%)$</th>
<th>Lungs-tumor $V_{20%\text{ Gy}}(%)$</th>
<th>Normal tissue $V_{20%\text{ Gy}}(%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4P102</td>
<td>Dtransform</td>
<td>rcfnSub1</td>
<td>Pinnacle</td>
<td></td>
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<tr>
<td>37</td>
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<td></td>
</tr>
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<td>2.5</td>
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<td>2.5</td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
4.4.3 Conclusion

The above results for the two patients showed that the DME for the OARs heart, lungs (P4P101), normal tissue and esophagus (P4P102) was reduced when the PTV was used as a planning target. These reductions were clinically significant (>2%) for P4P102 esophagus V45, heart V10, and P4P101 normal tissue V10.

4.5 Comparison of dose mapping algorithm at 4×4×4 mm$^3$

A lot of research work has been done on choosing an optimal dose grid size for dose computation [54] [55] [56]. For planning purposes on a static geometry, sufficient dose grid resolution is the resolution at which dose interpolation is a sufficient approximation of dose at all points in the geometry [57]. Dempsey has found that at dose grid size < 2.5 mm point-based dose computation algorithms converge with volume-based dose computation algorithms and an isotropic dose grid with <2.5 mm is sufficient to prevent dose errors larger than one percent. By extension, for deformable dose mapping, sufficient resolution is that at which interpolation introduces insignificant errors.

In this section, I study the effect of changing the dose grid size to 4 mm on dose mapping error for the 11 patients.

4.5.1 Method

The same treatment plans used in Section 4.3.3 were used for this sub-aim, except the dose grid size was changed to 4 mm by the following procedures for each patient.

To ensure consistency with the 2x2x2 mm$^3$ results and save computation time, the 4x4x4 mm$^3$ MC dose results were created by re-binning (merging) the 2x2x2 mm$^3$ results. This was accomplished as follows: (1) The 2 mm per phase MC doses were multiplied by
their respective 2 mm per phase mass files (generated at the time the EMCM code was run in 4.3.3) to obtain the 2 mm per phase energy files. (2) For each energy file obtained from step (1), 2 mm energy voxels were merged to form the energy file at 4 mm resolution. (3) The same procedure was done on the mass files to obtain mass files at the 4 mm resolution. The 4 mm per phase irradiated doses were generated by dividing the energy files from (2) by the mass files from (3).

Once the 4 mm per phase MC doses were obtained, they were loaded into Pinnacle. Dtransform, Tri-linear (with sub-voxeling 1, 2, 3), and Pinnacle dose mapping codes were run to generate the 4D accumulated doses on the reference phase. Instead, the next paragraph explains the procedure by which the EMCM 4 mm accumulated dose was obtained for each patient plan. The 4D EMCM accumulated 4 mm per phase doses were generated by dividing the merged 2 mm per phase mapped energy voxels by the merged 2mm per phase mapped mass voxels. Total 4D 4 mm EMCM doses accumulated on the reference phase were generated by adding the per phase accumulated doses. The EMCM mapped dose at 2x2x2 \( mm^3 \) was considered the gold standard algorithm for comparison. 4D dose comparison metrics were the same used in Section 4.3.3. Like the analysis that were done on the results in previous sections, any differences between DVH volume indices that are > 2% and > 1 Gy for DVH dose indices were considered clinically significant.

4.5.2 Results

Table 10 shows the \( 4 \times 4 \times 4 \ mm^3 \) and \( 2 \times 2 \times 2 \ mm^3 \) 4D-DVHs for patient P4P100 (on the left column), on the right are tables for each patient with data that corresponds to the absolute difference in OAR 4D-DVH volume indices with respect to EMCM \( 2 \times 2 \times 2 \ mm^3 \).
The data under the $4 \times 4 \times 4 \text{ mm}^3$ header represents the absolute difference in OAR 4D-DVH indices at $4 \times 4 \times 4 \text{ mm}^3$ for EMCM, N1 (Trilinear), N3 (Trilinear with sub-voxeling n=3), and Pin (Pinnacle) with respect to EMCM $2 \times 2 \times 2 \text{ mm}^3$. The data under the $2 \times 2 \times 2 \text{ mm}^3$ header represents the absolute difference in OAR 4D-DVH indices for N1, N3, and Pinnacle at $2 \times 2 \times 2 \text{ mm}^3$ with respect to EMCM $2 \times 2 \times 2 \text{ mm}^3$. Similar data for the rest of the patients are presented in Appendix VI [Table 15]. Table 11 lists the tumor D98 absolute differences for both dose grid sizes with respect to EMCM $2 \times 2 \times 2 \text{ mm}^3$.

Table 10: 4D-DVHs of the accumulated dose on the reference phase for patient P4P100 using $4 \times 4 \times 4 \text{ mm}^3$ and $2 \times 2 \times 2 \text{ mm}^3$ on the left. On the right are tables for each patient with data that corresponds to the absolute difference in OAR 4D-DVH volume indices with respect to EMCM $2 \times 2 \times 2 \text{ mm}^3$ for both dose grid sizes for EMCM, N1, N3, and Pinnacle dose mapping algorithms.
For all OARs for patients P4P100, P4P103, P4P104, P4P106, P4P110, P4P114, and the MD-Anderson patient, the DMEs were not clinically significant for the listed DIM methods for both dose grid sizes.

For Patient P4P102, the DMEs at $4 \times 4 \times 4\ mm^3$ for the cord $D_{1\%}$ and normal tissue $V_{20\text{Gy}}$ were clinically significant and were reduced to non-clinically significant values when a dose grid of $2 \times 2 \times 2\ mm^3$ was used. The esophagus $V_{35\text{Gy}}$ EMCM DME was clinically significant; there might be two reasons for the DIM DMEs at $4 \times 4 \times 4\ mm^3$, one of them is the 4D-dose interpolation error inherited in the DIM methods and the difference in the planned dose DVHs at both dose grid sizes which suggests that the 4 mm dose grid is insufficient resolution for treatment planning dose calculation [Figure 31]. The difference between the original planned doses at both dose grid sizes for the esophagus might have been propagated to cause a clinically significant error for the EMCM DME. Similar interpretation could be applied on patient P4P105 cord $D_{1\%}$ DME [Figure 32], P4P101 normal tissue $V_{10\text{Gy}}$ [Figure 33], P4P107 tumor $D_{98\%}$, cord $D_{1\%}$, and esophagus $V_{25\text{Gy}}$ [Figure 34], and the MD-Anderson patient tumor $D_{98\%}$. 
Figure 31: DVHs of (1/10)\(^\text{th}\) planned dose on phase 0\% for both dose grid sizes for P4P102.
Figure 32: DVHs of \((1/10)\times\)planned dose on phase 0\% for both dose grid sizes for P4P105.
Figure 33: DVHs of (1/10)*planned dose on phase 0% for both dose grid sizes for P4P101.
Figure 34: DVHs of (1/10)*planned dose on phase 0% for both dose grid sizes for P4P107.
To further analyze the results, [Table 11] lists the tumor 4D-D98 (cGy) Trilinear N1, N3, and Pinnacle absolute differences with respect to EMCM for both dose grid sizes. For patients P4P100, P4P102, P4P106, and P4P110 the DMEs were not clinically significant between the two dose grid sizes. For the same dose mapping method EMCM, the DME was clinically significant between the two dose grid sizes for patients P4P101, P4P103, and P4P114. For these patients, the DVH plots of the original planned dose at both dose grid sizes did not show any large differences for the tumor $D_{98\%}$. Figure 33, Figure 36, and Figure 37, thus this EMCM DME might be due to the resampling of the 4D-EMCM 4mm from the 4D-EMCM 2mm.
Table 11: Tumor 4D-D98 (cGy) Trilinear (N=1,3), Pinnacle, and EMCM absolute differences with respect to EMCM at $2 \times 2 \times 2$ mm$^3$ for all the patients for both dose grid sizes.

<table>
<thead>
<tr>
<th>Tumor D98 in cGy</th>
<th>$4 \times 4 \times 4$ mm$^3$</th>
<th>$2 \times 2 \times 2$ mm$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETM</td>
<td>N1</td>
</tr>
<tr>
<td>P4P100</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>P4P101</td>
<td>166</td>
<td>51</td>
</tr>
<tr>
<td>P4P102</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>P4P103</td>
<td>193</td>
<td>16</td>
</tr>
<tr>
<td>P4P104</td>
<td>51</td>
<td>83</td>
</tr>
<tr>
<td>P4P105</td>
<td>30</td>
<td>68</td>
</tr>
<tr>
<td>P4P106</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>P4P107</td>
<td>190</td>
<td>242</td>
</tr>
<tr>
<td>P4P110</td>
<td>0.35</td>
<td>17</td>
</tr>
<tr>
<td>P4P114</td>
<td>119</td>
<td>51</td>
</tr>
<tr>
<td>MD-And</td>
<td>202</td>
<td>286</td>
</tr>
</tbody>
</table>
Figure 36: DVHs of \((1/10)^*\)planned dose on phase 0\% for both dose grid sizes for P4P103.
Figure 37: DVHs of \((1/10)^\text{*planned dose} \) on phase 0\% for both dose grid sizes for P4P114.

Table 12 shows the DME RMS at both dose grid sizes for all patients for tumor $D_{98\%}$, lung $V_{200\text{Gy}}$, and cord $D_{1\%}$. The DMEs RMS were reduced at $2 \times 2 \times 2 \text{mm}^3$ for the tumor, cord, and lung $V_{200\text{Gy}}$.

Table 12: DMEs RMS for all patients at the two dose grid sizes for the tumor, lung, and cord.

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th>N3</th>
<th>Pin</th>
<th>N1</th>
<th>N3</th>
<th>Pin</th>
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<tbody>
<tr>
<td><strong>Tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{98%}$</td>
<td>120</td>
<td>131</td>
<td>137</td>
<td>73</td>
<td>73</td>
<td>134</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{200\text{Gy}}$</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.43</td>
<td>0.43</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Cord(cGy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{1%}$</td>
<td>106</td>
<td>109</td>
<td>108</td>
<td>17</td>
<td>18</td>
<td>35</td>
</tr>
</tbody>
</table>
Appendix VI [Table 16-Table 17] contains more 4 mm dose grid 4D data results for OARs and tumor for all dose mapping algorithms compared to EMCM.

4.5.3 Conclusion

The above results showed that, as the dose grid size becomes smaller, the RMS for the DME for DIM over all the patients becomes smaller for the tumor 4D-$D_{98\%}$, lung $V_{20\%}$, and cord $D_{1\%}$. The clinical effect of changing the dose grid size from 4 mm to 2 mm on dose mapping was small for OARs and was patient specific.
5  A Distance to Dose Difference tool for estimating the Required Spatial Accuracy of a Displacement Vector Field

As mentioned in previous chapters, accuracy of dose mapping depends on the accuracy of the DVF used in the mapping process and on the local dose gradient in the irradiated geometry. Some DVF errors are inconsequential. For example, if a registration DVF error occurs in a uniform dose region [Figure 38a], then the resultant dose error is small. Conversely, if a registration error occurs in a high dose gradient, such as in the penumbra region, [Figure 38b] then resultant dose error can be large.

Figure 38: Illustration of the effect of the displacement vector field (DVF) errors on dose mapping errors. On each panel, the green arrows are possible displacement vectors for mapping information from the irradiated image to the reference image. The red arrow represents the DVF error. In (a), the error occurs in a uniform dose region; hence the dose mapping error is minimal. In (b), the error occurs in a dose gradient region, resulting in a large dose mapping error.
One can exploit this relationship between DVF accuracy and dose mapping accuracy to determine how large of an DVF error could be tolerated before it could introduce a given dose error. For example, if the desired dose mapping accuracy is 2% of the local dose, then DVF errors are relevant only if the dose at an incorrectly mapped point is >2% different from the dose at the "correctly" mapped dose point. This suggests that a metric which provides an upper bound of allowable DVF uncertainty can be developed based upon a distance to difference (DTD) analysis, where the distance to a dose difference threshold in the irradiated geometry is evaluated.

The DTD concept is unique in that it does not require knowledge of the DVF. Instead, DTD indicates how large a DVF error can be before the DVF error could introduce a pre-determined maximum tolerable dose mapping error. The DTD threshold is adaptable based on the desired evaluation; DTD can be for a given percentage of the local dose, given percentage of maximum dose, for any arbitrary absolute dose difference, or even to an absolute dose level.

This chapter introduces the DTD concept which was published as a part of this dissertation work [58] (See Appendix I), demonstrates its use for mapping dose between two phases of a 4D lung plan, and compares the DTD with a method based on the gradient of the dose distribution.
5.1 Method and materials

5.1.1 DTD algorithm

Although a computer algorithm could be written that directly computed DTD, the DTD algorithm [Figure 39] used in this work is developed using a technique similar to that used for distance to agreement (DTA) analysis.

DTA utilizes two dose distributions, A and B, on a common coordinate system which are to be compared. For each dose value at a point in distribution A, the DTA is the shortest distance that must be traversed in B to have an equivalent dose value. This concept can be extended to a DTD concept. DTD utilizes a single dose distribution as input since the desire is to determine the minimum distance one must traverse in this dose distribution to observe a dose difference greater than the tolerance. For example, if the desired dose accuracy is n=2% of the local dose, then beginning with dose distribution A, a dose distribution B+ is created by multiplying the dose values in A by \((1+n/100)=1.02\). The DTA at each point between A and B+ is then determined, producing DTA+. Similarly, a dose distribution B- is created by multiplying the dose values in A by \((1-n/100)=0.98\) with the DTA at each point between A and B- determining DTA-. At each point, the DTD to ensure a maximum of an n% local dose error will be the minimum of (DTA+, DTA-). If one would like to know the DTD in terms of an absolute (# Gy) dose value, e.g. \(\Delta D= 0.02DRx\), then \(B+ =A+\Delta D\) and \(B- =A-\Delta D\) respectively in the computation of DTA+ and DTA-. 
In this study, the DTD is based upon an in-house developed C++ DTA algorithm. The DTA algorithm progressively searches in shells of increasing radius (number of voxels) for the dose agreement point in matrix $B^\pm$ which surrounds the point of interest from matrix $A$. Internally, the DTA algorithm tri-linear interpolates the dose to a $1\times1\times1 \ mm^3$ resolution in the search matrix to reduce errors inherent to the discrete voxel-based DTA algorithm used. [Chapter 6] describes an algorithm that is both more accurate and more efficient.
than the algorithm used in this chapter. In fact, completion of this study inspired the
development of the [Chapter 5] algorithm. Similar DTA algorithms are described in
references[59] [60] [61] [62].

5.1.2 DTD example

To demonstrate the utility of the DTD, an intensity modulated radiation therapy
(IMRT) lung treatment plan is generated using Pinnacle³ (Philips Medical Systems,
Fitchburg, WI). The plan uses an internal target volume (ITV), generated from the union of
the clinical target volume (CTV’s) on all breathing phases of a 10 phase 4DCT (phase 0%
to 90%) plus a 0.5 cm ITV-planning target volume (PTV) margin. The treatment plan is
generated on phase 0% (end of inhale). The minimum prescribed dose to the target is 66
Gy using direct machine parameters optimization IMRT optimization with a 4×4×4 mm³
dose grid resolution. The DTD is computed for both 4×4×4 mm³ and 2×2×2 mm³ dose
grid resolutions based on the collapsed-cone dose algorithm dose values. The figures
show the 4×4×4 mm³ results unless otherwise noted.

Following planning, the DTD is determined for n=2% of the local dose computed on
phase 0% (DTD2%), and for ΔD =1.32 (DTD1.32Gy) and 3.30 Gy (DTD3.30Gy),
Corresponding with 2% and 5% of the prescription dose. These values are chosen in
accordance with suggested dose accuracy values listed in ICRU report #62.5

To visualize and analyze DTD, the externally computed DTD values are loaded into
Pinnacle as a beam in a separate trial and the monitor units are adjusted so that dose
values can be interpreted as distance values (in mm). This enables viewing of isoDTD
lines on the patient’s anatomy and creation of DTD volume histograms (DTDvh) using pre-
existing Pinnacle tools.
5.1.3 Comparison with dose gradient

An approach similar to the DTD is to evaluate the gradient of the 3D dose distribution then divide the desired dose tolerance value by the dose gradient. This method is called TDG, for tolerance divided by gradient. The 3D-dose gradient is computed using the central difference method, yielding gradients in the x, y, and z directions. TDG values are computed in two ways, one using the magnitude of the 3D dose gradient (TDG3D) and the other using the maximum of the dose gradient [\(\frac{\partial D}{\partial x}, \frac{\partial D}{\partial y}, \frac{\partial D}{\partial z}\)] in a given direction (TDGmax). The TDG method is compared with the DTD method by comparing color wash distributions, DTDvhs with TDGvhs, and plotting point-by-point DTD values with respect to TDG values.

5.2 Findings

Figure 40 shows the isodose lines on phase 0% for the IMRT plan overlaid on a transverse slice of the patient’s anatomy. This same transverse slice is used to show the DTD-values in the later figures. Figure 41(a) shows the DTD2% overlaid on this transverse slice. The maximum DTD2% value observed inside the CTV is 6 mm, with values of 1 to 4 mm surrounding the CTV. Within the entire image, DTD2% values as low as 0.1 mm are observed.
Figure 40: Isodose lines on phase 0% on a single transverse slice of the IMRT plan used in this study. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange).

Figure 41(b) shows color wash isoDTD’s for the DTD1.32Gy. Outside the irradiated region, the plan can tolerate up to 10 mm DVF errors. Inside the irradiated region, but outside the CTV in large dose gradient regions, DVF errors between 0.5-1 mm can be tolerated. Inside the CTV, the plan can tolerate up to 4 mm DVF error. Similarly, Figure 41(c) shows color wash isoDTD’s for the DTD3.3Gy. The DTD3.30Gy differs from the DTD1.32Gy demonstrating the variation of DTD with the required dose accuracy. Outside the irradiated region, the plan can tolerate up to 10 mm DVF errors. Inside the irradiated region, but outside the CTV in large dose gradient regions, DVF errors between 1-8 mm can be tolerated. Inside the CTV, the plan can tolerate up to 10 mm DVF errors.
Figure 41: Color wash of DTD values overlaid on a transverse slice of the patient anatomy. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm. (a) DTD2%; tolerance is 2% of the local dose value (b) DTD1.32Gy; tolerance is 1.32 Gy (2% of the prescription dose) and (c) DTD3.30Gy; tolerance is 3.30 Gy (5% of the prescription dose). On this slice, in (a), outside the treatment region DTD values range from 0.1 to 1 mm, around the CTV values range from 1 to 4 mm, and inside the CTV DTDs up to 6 mm are observed. In (b), inside the CTV volume the plan absorbs DVF 4 mm errors. In dose gradients around the CTV, 0.5 to 1 mm DVF errors are permitted, and outside the treatment region DVF errors up to 10 mm are tolerated. In (c), inside the CTV, 10 mm DVF error is permitted. In dose gradients around the CTV, 1 to 8 mm DVF errors are permitted, and outside the treatment region DVF errors up to 10 mm are tolerated.

These results suggest that accurate DVF’s are not needed for the whole image for dose mapping purposes. For the two DTD distributions calculated; both results show that in high dose gradient regions, spatial dose or DVF accuracy requirements are tight, whereas inside the CTV or outside the treatment region both requirements can be relaxed and the plan can absorb more errors. While isoDTDs overlaid on the patient’s anatomy allow visual identification of areas which are tolerant or intolerant to DVF errors, to statistically interpret the spatial dose or DVF accuracy requirements, the DTD can be plotted as function of the volume of any structure. Figure 42 shows an example DTDvhs for the CTV structure for the 3.30 Gy and 1.32 Gy dose difference DTD criteria. From
these graphs, one can read out the DVF accuracy required as a function of the percentage volume of the structure. While not as useful as 3D visualization of the DTD, these DTDvh's enable simple statistical analysis of DTD properties.

DTDs calculated based on the $2\times2\times2 \, mm^3$ dose grid resolution (not shown) look similar to the $4\times4\times4 \, mm^3$ results shown in [Figure 41]. DTD values should not vary significantly with dose grid resolution when the dose resolution is sufficient such that intermediate points can be tri-linear interpolated with errors small compared with the size of the DTD criteria. For points within the patient contour, the average DTD values computed at the $4\times4\times4 \, mm^3$ and $2\times2\times2 \, mm^3$ resolutions differ by less than 0.05 mm, with a root-mean-square difference of 0.7 mm. Figure 42 shows that differences in the 3.3 Gy CTV DTDvh values are less than 0.5 mm for the different dose matrix resolutions. The deviations are due to differences in dose values computed within the CTV for the different resolutions and due to limitations of the underlying DTA algorithm used.
Figure 42: CTV distance-to-difference volume histogram (DTDvh) for the DTD3.30Gy and DTD1.32Gy values. The DTD data indicates that ninety percent of the CTV can tolerate DVF errors up to 1.01 mm for $\Delta D = 1.32$ Gy and 2.8 mm for $\Delta D = 3.30$ Gy. 30% of the CTV can tolerate DVF errors up to 2.1 mm for $\Delta D = 1.32$ Gy and 6.6 mm for $\Delta D = 3.30$ Gy. Also plotted is the histogram of the dose tolerance divided by gradient (TDG) values for a 3.30 Gy dose tolerance, which indicates that 90% of the CTV tolerated DVF errors up to 5 mm, and 30% of the volume can tolerate up to 12 mm errors. DTD and TDG values shown are computed using a dose matrix resolution of $4 \times 4 \times 4 mm^3$, except for one 3.30 Gy DTD curve (noted as DTD3.30 Gy, 2 mm dose resolution) computed with a $2 \times 2 \times 2 mm^3$, dose matrix to show deviations caused by computing at a different dose resolution.

The $TDG^{3D}$ image for 3.30 Gy dose difference tolerance ($TDG_{3.30 Gy}^{3D}$) is shown in Figure 43. Qualitatively, this image is similar to the DTD3.3Gy [Figure 41c] in dose gradient regions, but differs in regions inside the CTV and outside the radiation beams where $TDG_{3.30 Gy}^{3D}$ indicates larger tolerances of DVF or spatial dose errors from the DTD method. Figure 44 compares the point-by-point DTD3.30Gy values with the $TDG_{3.30 Gy}^{3D}$ values for dose points within the patient contour. The banding in the DTD values is due to the $1 \times 1 \times 1 mm^3$ resolution used within the DTA algorithm. Generally, TDG values are
larger than DTD values for this case. Poor correlation between DTD3.30Gy and $TDG_{3,30\,Gy}^{3D}$ values is observed, especially for large values. Points with large $TDG_{3,30\,Gy}^{3D}$ values yet small DTD3.30Gy values are detected. The TDG is inversely proportional to the dose gradient. Because $TDG^{3D}$ uses the magnitude of the gradient vector, which can have small components in one direction but large components in others, it can overestimate permissible spatial dose errors in low dose gradient region. In high dose gradient region, the TDG can over- or underestimate spatial dose errors depending on the curvature of the dose distribution.

![Figure 43: Color wash of the TDG$^{3D}_{3,30\,Gy}$](image)

Small TDG values (1-4 mm) are observed inside the treated region excluding the CTV.
Figure 44: Scatter plot between the calculated DTD$_{3.30Gy}$ and the TDG$_{3.30Gy}$. Poor correlation between these quantities is observed, particularly at large values.

TDGmax, which uses the maximum dose gradient, has similar poor correlation with the DTD (not shown). Overall, the TDG method is limited in its ability to evaluate acceptable DVF errors.

5.3 Discussion

Current deformable image registration algorithm and associated DVFs are inherently inaccurate. Several groups have been working on estimating the accuracy / uncertainty in deformable image registration algorithms [63] [64] [20] [16] [65] [14] [17]; however little work has been done on finding the required spatial accuracy of a DVF. In this work, a simple algorithm is introduced to compute a distance to a dose difference tolerance that can be related to how accurate the DVF used in dose mapping has to be to ensure that the specified dose accuracy tolerance is not violated.
Current deformable image registration algorithms focus on creating an as-accurate-as-possible registration for an entire image or restrict over a given region of interest. The results of this work indicate that for dose mapping purposes, accurate registration is needed in high dose gradient regions, with less accuracy in uniform dose areas. Theoretically, a DIR algorithm could be written which emphasizes accuracy in dose gradient regions via methods such as voxel weighting, location of spline-interpolant knots, etc.

For simplicity, the example presented in this work evaluated the DTD between phases of a 4D lung treatment plan. Specifically, the DTD estimates the required DVF spatial accuracy needed to map dose delivered on the end of inhale breathing phase (phase 0%) to any of the other breathing phases. The tolerance values are selected as if the full treatment delivery occurred on the phase 0% image set. If dose delivery on multiple 4D breathing phases is considered, the sum of the DVF induced dose mapping errors (from the different mappings) would need to be less than the tolerance value. If the DTD dose error tolerance is equi-distributed among the breathing phases, the dose delivered and DTD threshold values change by the same fraction, resulting in the same DTD for the phase 0% to phase N% mappings as given above. Alternatively, the DTD dose error tolerance could be unequally distributed among the different image sets, while still requiring that the total dose error induced is less than the threshold. This complex analysis is left for further study.

The example presented in this work utilized DTD tolerance values with respect to target dose values. However, the DTD concept is general and DTDs can be computed to
arbitrary, even region of interest specific tolerances. For example, for critical structures, an appropriate tolerance could be the maximum tolerated dose.

The DTD tool provides qualitative utilities when interfaced with a treatment planning system; DTD can be visualized as iso-DTD lines/color washes that provide the planner with the ability to see geographical maps of tolerated and un-tolerated DVF errors before using a specified DVF with a given uncertainty for dose mapping. DTD-volume histograms can provide volume-based statistical error analysis for targets, organs at risk, or arbitrary regions of interest in an image.

The DTD tool is not limited to estimating the spatial accuracy of a DVF. For a given dose difference tolerance (absolute or %) one can determine the distance error that can be tolerated before violating the specified dose accuracy. For a CTV, the DTD can be used as a first estimate of how large a setup error can be before introducing a clinically significant dose error. Similarly, knowledge of the maximum tolerated setup error can be used in plan evaluation, possibly affecting CTV-to-PTV or organ at risk-to-planning risk volume (PRV) planning margins.

5.4 Summary

This chapter introduces a new method which estimates how large a DVF error can be tolerated before introducing a potentially clinically significant error in the dose mapping processes. The required DVF spatial accuracy will depend on the particular dose distribution. For dose mapping, DVFs accuracy must be highest in dose gradient regions, while less accurate DVFs can be tolerated in uniform dose regions. The DTD tool can be used as a first estimate of DVF required spatial accuracy and can be applied to other areas when the distance to a dose difference tolerance is required to be known.
6  A continuous 3D DTA algorithm

In chapter 5, the distance to dose difference (DTD) tool was introduced to estimate the required spatial accuracy of a displacement vector field for 4D dose calculations. As implemented, the DTD code is based on a pair of distance to agreement (DTA) calculations. In chapter 5, an in-house DTA code that evaluates and interpolates on the discretely valued dose distribution was used. This method suffers from discretization and interpolation errors, causing discontinuities and inaccuracies in the determination of the required spatial accuracy of a DVF.

In this chapter, a 3D gamma continuous code I wrote is described of which the DTA portion can be utilized for discretization and interpolation error-free DTD calculations. While the discrete DTA algorithm relies on an exhaustive point-by-point search in the calculated dose distribution and applies interpolation to find the point with the same measured dose point, the continuous 3D DTA algorithm finds the closest geometric distance between the two distributions by dividing the calculated (reference) dose distributions into simplexes. The closest distance with the same dose point between any test dose point and these simplexes can be directly computed using matrix multiplication and inversion without the need of interpolating.
The flow work of the code, some QA test cases, and comparison results between discrete DTA (in house code) and continuous DTA (using the new code) are discussed in this chapter.

6.1 Gamma Index

The gamma index [60] has been used in medical physics practice in the comparison of two dose distributions (e.g. measured and calculated) as a measure of agreement between the two dose distributions for QA purposes. The gamma index is given by the following equation:

\[
\gamma(\vec{\rho}_0) = \min_{\vec{p}} \left( \sqrt{\frac{|\vec{p} - \vec{p}_0|}{\delta d_0^2} + \frac{(D(\vec{p}) - D_0(\vec{\rho}_0))^2}{\delta D_0^2}} \right) \tag{7}
\]

where \(\delta d_0^2\) is the distance criterion in mm and \(\delta D_0^2\) is the percentage dose difference criteria. Agreement is defined as number of dose points in a required region of interest that have gamma \(\leq 1\) and typical passing criteria requires \(90\%\) of points with \(\gamma \leq 1\). Typical distance/dose tolerance values are 3 mm / 3%.

When the dose difference term in the above equation is zero \((D(\vec{\rho}) - D_0(\vec{\rho}_0))^2\), gamma index becomes a DTA index.

6.2 Continuous gamma

Continuous gamma [59] relies on geometry principles to compute the gamma index. It is based on finding the closest distance from a test point to reference surface. A reference surface can be divided into simplexes. A simplex with \(n=1\) is a line, \(n=2\) is a plane and \(n=3\) is a tetrahedron.
6.2.1 2D continuous gamma

Figure 45 demonstrates finding geometric gamma for a two dimensional case,

![Diagram of gamma calculation](image)

With reference to Figure 45, assume that the gamma index is being computed for the top left grid location. The test image intensity (i.e., dose) at that point is denoted by \( D_{\text{test}} \). Surrounding grid squares may be divided into upper and lower triangles, as indicated by the shading of the two regions. Consider the upper triangle associated with the grid offset \((i,j)\). [In Figure 45, \( i = 2 \) and \( j = -1 \)]. Coordinates \((\alpha, \beta)\) denote an interior point within this triangle. The units of \( \alpha \) and \( \beta \) are pixels. Interior points have \( 0 < \alpha, \beta < 1 \) with \( \alpha + \beta < 1 \). Edge points have \( 0 \leq \alpha, \beta \leq 1 \) with \( \alpha = 0, \beta = 0 \) or \( \alpha + \beta = 1 \).

Denote the reference image dose at offset \((i,j)\) by \( D_{i,j} \), the reference image dose at offset \((i+1,j)\) by \( D_{i+1,j} \), and the reference image dose at offset \((i, j+1)\) by \( D_{i,j+1} \). Assuming that dose may be linearly interpolated within the triangle, the reference image dose \( D_{\alpha, \beta} \) at point \((\alpha, \beta)\) may be expressed as:
\[ D_{\alpha,\beta} = (1 - \alpha - \beta).D_{i,j} + \alpha. D_{i+1,j} + \beta. D_{i,j+1} \]  \hspace{1cm} (8)

And the reference distance \( p \) to get to point \((\alpha, \beta)\) may be expressed as:

\[ p_{\alpha,\beta} = (1 - \alpha - \beta) \times p_{i,j} + \alpha \times p_{i+1,j} + \beta \times p_{i,j+1} \]  \hspace{1cm} (9)

And the value of \( \Gamma^2 \) at \((\alpha, \beta)\) is given by:

\[ \Gamma^2_{\text{test}} = \left( \frac{100}{D_{\text{crit}}} \right)^2 \times \left( \frac{D_{\alpha,\beta} - D_{\text{test}}}{D_{\text{test}}} \right)^2 + \left( \frac{s_{\text{pixel}}}{s_{\text{crit}}} \right)^2 \times \left[ (i + \alpha)^2 + (j + \beta)^2 \right] \]  \hspace{1cm} (10)

where \( s_{\text{pixel}} \) is the pixel size, \( s_{\text{crit}} \) is the distance criterion in pixel units, and \( D_{\text{crit}} \) is the dose criterion. For the current application (computing DTA), \( s_{\text{pixel}} = 4 \text{ mm}, s_{\text{crit}} = 3\text{mm}, \) and \( D_{\text{crit}} = 0.001\% \). The later term makes \( \Gamma \) nearly equivalent to the DTA index, therefore, \( \Gamma \) and DTA are used interchangeably below. Using coordinate points instead of \( i \) and \( j \) offsets, such as in the triangle case we have 3 vertices: \( P_1, P_2 \) and \( P_3 \) for the reference image and \( P_3 \) for the test image equation 10 can be rearranged into:

\[ r^2 = \kappa^2 \times [(1 - \alpha - \beta) \times d_1 + \alpha \times d_2 + \beta \times d_3 - d_0]^2 + \]
\[ \lambda^2 [(1 - \alpha - \beta) \times P_{1x} + \alpha \times P_{2x} + \beta \times P_{3x} - P_{ox}]^2 + [(1 - \alpha - \beta) \times P_{1y} + \alpha \times P_{2y} + \beta \times P_{3y} - P_{oy}]^2 + [(1 - \alpha - \beta) \times P_{1z} + \alpha \times P_{2z} + \beta \times P_{3z} - P_{oz}]^2 \]  \hspace{1cm} (11)

where \( \kappa = \frac{1}{D_{\text{crit}} \times d_0} \) and \( \lambda = \frac{s_{\text{pixel}}}{s_{\text{crit}}} \).

Setting the derivatives of \( r^2 \) with respect to \( \alpha \) and \( \beta \) equal to zero gives two linear equations which can be solved for \( \alpha \) and \( \beta \).

\[ \frac{\partial r^2}{\partial \alpha} = a_1. \alpha + b_1. \beta + d_1 \]  \hspace{1cm} (12)

where \( a_1 \) and \( b_1 \) are the coefficients of \( \alpha \) and \( \beta \) in equation 12 and \( d_1 \) is a constant.
\[
\frac{\partial^2 z}{\partial \beta^2} = a2 \cdot \alpha + b2 \cdot \beta + d2
\]  

(13)

where \(a2\) and \(b2\) are the coefficients of \(\alpha\) and \(\beta\) in equation 13 and \(d2\) is a constant.

\[
a1 = 2k^2 \times (D_2 - D_1)^2 + 2\lambda^2 \times (P_{2x} - P_{1x})^2 + 2\lambda^2 \times (P_{2y} - P_{1y})^2 + 2\lambda^2 \times (P_{2z} - P_{1z})^2
\]

\[
\times (P_{2x} - P_{1x})^2
\]  

(14)

\[
b1 = 2k^2 \times (D_2 - D_1) \times (D_3 - D_1) + 2\lambda^2 \times (P_{2x} - P_{1x}) \times (P_{3x} - P_{1x}) + 2\lambda^2 \times (P_{2y} - P_{1y}) \times (P_{3y} - P_{1y}) + 2\lambda^2 \times (P_{2z} - P_{1z}) \times (P_{3z} - P_{1z})
\]

\[
\times (P_{2x} - P_{1x}) \times (P_{2y} - P_{1y}) + 2\lambda^2 \times (P_{2z} - P_{1z}) \times (P_{3z} - P_{1z})
\]  

(15)

\[
d1 = 2k^2 \times (D_2 - D_1) \times (D_1 - D_0) + 2\lambda^2 \times (P_{2x} - P_{1x}) \times (P_{1x} - P_{0x}) + 2\lambda^2 \times (P_{2y} - P_{1y}) \times (P_{0y} - P_{1y}) + 2\lambda^2 \times (P_{2z} - P_{1z}) \times (P_{0z} - P_{1z})
\]

\[
\times (P_{1x} - P_{0x})
\]  

(16)

Similarly, the coefficients of \(\alpha\) and \(\beta\) and the constant in equation 13 are given by:

\[
a2 = 2k^2 \times (D_3 - D_1) \times (D_2 - D_1) + 2\lambda^2 \times (P_{3x} - P_{1x}) \times (P_{2x} - P_{1x}) + 2\lambda^2 \times (P_{3y} - P_{1y}) \times (P_{2y} - P_{1y}) + 2\lambda^2 \times (P_{3z} - P_{1z}) \times (P_{2z} - P_{1z})
\]

\[
\times (P_{3y} - P_{1y}) \times (P_{2y} - P_{1y}) + 2\lambda^2 \times (P_{3z} - P_{1z}) \times (P_{2z} - P_{1z})
\]  

(17)
\[
b2 = 2k^2 \times (D_3 - D_1)^2 + 2\lambda^2 \times (P_{3x} - P_{1x})^2 + 2\lambda^2 \times (P_{3y} - P_{1y})^2 + 2\lambda^2 \times (P_{3z} - P_{1z})^2
\]
\[
d2 = 2k^2 \times (D_3 - D_1) \times (D_1 - D_0) + 2\lambda^2 \times (P_{3x} - P_{1x}) \times (P_{1x} - P_{0x}) + 2\lambda^2 \times (P_{3y} - P_{1y}) \times (P_{1y} - P_{0y}) + 2\lambda^2 \times (P_{3z} - P_{1z}) \times (P_{1z} - P_{0z})
\]

Solving for \( \alpha \) and \( \beta \),
\[
\alpha = \frac{b1 \cdot d1 - b2 \cdot d1}{a1 \cdot b2 - a2 \cdot b1}
\]
\[
\beta = \frac{a2 \cdot d1 - a1 \cdot d2}{a1 \cdot b2 - a2 \cdot b1}
\]

If the resulting values correspond to an interior point \((0 < \alpha, \beta < 1 \text{ with } \alpha + \beta < 1)\), that point gives the candidate minimum value for \( \gamma \) within the triangle. Minima on the triangle edges can be found similarly (edge points have \(0 \leq \alpha, \beta \leq 1\) with \(\alpha = 0, \beta = 0\) or \(\alpha + \beta = 1\)). The overall minimum for the triangle is the minimum of these points and the doses \(d_{i,j}, d_{i+1,j}\) and \(d_{i,j+1}\). Iteration through all offsets \((i, j)\) out to the specified search distance gives the global minimum value of \( \gamma \).

\[
r_{\text{triangle}} = \min(r_{\text{interior}}, r_{\text{edge1}}, r_{\text{edge2}}, r_{\text{edge3}})
\]

For a line case \((n=1)\), equation 6 becomes:
\[
r^2 = \kappa^2 \times [(1 - \alpha) \times d_1 - d_0]^2 + \lambda^2 \times [(1 - \alpha) \times P_{1x} + \alpha \times P_{2x} -
\]

\[
100
\]
\[
P_{ox}^2 + [(1 - \alpha) \times P_{1y} + \alpha \times P_{2y} - P_{oy}]^2 + [(1 - \alpha) \times P_{1z} + \alpha \times P_{2z} - P_{oz}]^2
\]

After setting \( \frac{dP^2}{d\alpha} = 0 \), separating the equation to get coefficient of \( \alpha \) and solving for \( \alpha \), we get \( \alpha = -c/a \), where \( a \) is the coefficient of \( \alpha \) in the linear equation and \( c \) is the constant part in the equation. After that, the value of \( \alpha \) is substituted in equation 23 to get the square of min gamma.

### 6.2.2 3D continuous gamma

The 3D derivation is similar to the 2D derivation, except \( n=3 \), the highest order simplex that must be considered is a tetrahedron, and the 3D reference dose distribution voxels are each divided into 5 tetrahedrons [Table 13]. T1 is the central tetrahedron with all sides equal; it has a volume 1/3 and vertices: (1,0,0), (0,1,0), (0,0,1), (1,1,1). T2 has volume 1/6 and vertices: (0,0,0) [pyramid apex], (1,0,0), (0,1,0), (0,0,1). T3 has volume 1/6 and vertices: (1,0,1) [pyramid apex], (0,0,1), (1,1,1), (1,0,0). T4 has volume 1/6 and vertices: (1,1,0) [pyramid apex], (0,1,1), (1,1,1), (1,0,0). T5 has volume 1/6 and vertices: (0,1,1) [pyramid apex], (0,0,1), (1,1,1), (0,1,0). As a check, in the above set of 20 vertices, the apexes should appear once. All other vertices should appear 4 times: 4 + (20 -4)/4 = 8.

**Table 13: summary of tetrahedrons spatial coordinates and volume information.**

<table>
<thead>
<tr>
<th># of tetrahedron</th>
<th>Vertices coordinate</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1,0,0)apex</td>
<td>(0,1,0)</td>
</tr>
<tr>
<td>2</td>
<td>(0,0,0)apex</td>
<td>(1,0,0)</td>
</tr>
<tr>
<td>3</td>
<td>(1,0,1)apex</td>
<td>(0,0,1)</td>
</tr>
<tr>
<td>4</td>
<td>(1,1,0)apex</td>
<td>(0,1,1)</td>
</tr>
<tr>
<td>5</td>
<td>(0,1,1)apex</td>
<td>(0,0,1)</td>
</tr>
</tbody>
</table>
The equation for gamma continuous for the 3D case is written as:

$$r^2 = \kappa^2 \times \left[ (1 - \alpha - \beta - \omega) \times d_1 + \alpha \times d_2 + \beta \times d_3 + \omega \times d_4 - d_0 \right]^2$$

$$+ \lambda^2 \left[ (1 - \alpha - \beta - \omega) \times P_1 + \alpha \times P_2 + \beta \times P_3 + \omega \times P_4 - P_{ox} \right]^2$$

where \( \omega \) is the z-coordinate in pixel units. The solution in this case is more complicated than the 1D and 2D, after setting \( \frac{dv^2}{d\alpha} = 0, \frac{dv^2}{d\beta} = 0, \frac{dv^2}{d\omega} = 0 \), we can solve for \( \alpha, \beta \) and \( \omega \).

The 3D gamma continuous computer algorithm is divided into 5 subroutines Figure 46: (1) compute gamma for a point, (2) compute gamma for a line, (3) compute gamma for a triangle, (4) compute gamma for a tetrahedron, and (5) compute gamma continuous. The compute gamma continuous subroutine is the primary subroutine. It sets the coordinates in the 3D dose distribution points and calls the tetrahedron routine to compute gamma for the 5 tetrahedrons. The tetrahedron routine calls the triangle function 4 times for each tetrahedron, since there are 4 triangles in a tetrahedron. The triangle function calls the line function 3 times for each triangle, since there are 3 lines to form a triangle and finally the line function calls the point function 2 times for each line, since 2 points form a line.
Figure 46: flow chart for the 3D gamma continuous code.
6.3 3D gamma QA test cases and results

The tests were conducted on 3×3×3 known dose phantoms generated in Matlab. Some test cases were: Input same dose file, DTA is zero; Apply known displacement shifts to the evaluated phantom, DTA equals the shift; Check computing DTA on phantom edges; Swab images and compute DTA again; Transpose matrices, DTA should not change.

6.3.1 Test case one

The purpose of this test case is to test the code when both the test and the reference dose distributions are the same. In this case, the DTA must equal zero Figure 47.
6.3.2 Test case two

In this test case, voxel (1,2,1) in the test image is shifted one voxel in the x-direction to generate the reference image. Figure 48 shows reference image (a), test image (b), and computed DTA (c). From the DTA figure, we can report that the DTA for voxel (1,2,1) is one pixel units as expected, since that voxel was shifted one voxel in one direction. For voxel (2,2,1) in the test image, although, that voxel was also shifted one voxel, the DTA reported was not one pixel since, the code finds the minimum gamma along the line between voxel (2,1,1) and voxel (3,2,1) where the minimum distance was computed as follows:
minP = 0.5* \left( (3 - 2)^2 + (2 - 10)^2 + (1 - 1)^2 \right) = 0.7 \text{ pixel, where } \alpha = 0.5.

(a)
(b)
(c)

Figure 48: 14 (a) Reference image showing all dose values are the same except one voxel in the middle has a value of 4. (b) Test image with all voxels have value of 3 except the second voxel in the first row has a value of 4. (c) is the computed DTA in pixel units.

6.4 Comparison with discrete DTA code

Test case two was repeated, but this time using the in-house discrete code used in Chapter 5 to compute DTD. From Figure 49, (d) the discrete DTA code reported DTA values of one pixel for both voxel (1,2,1) and voxel (2,2,1), whereas continuous DTA reported a DTA value of 0.7 pixel for voxel (2,2,1), which shows that the discrete DTA failed
to detect any interior DTA values which will degrade the accuracy of the computed DTA values.

![Figure 49](image)

Figure 49: (a) Reference dose showing all dose values are the same except one voxel in the middle has a value of 4. (b) Test dose with all voxels have values of 3 except the second voxel in the first row has a value of 4. (c) is the computed DTA in pixel units using DTA continuous code and (d) is the computed DTA in pixel units using discrete DTA code.

### 6.5 Conclusion

In comparison with discrete DTA on a phantom case, continuous DTA proved to be more accurate than discrete DTA. 3D DTA continuous was developed, proved to be more accurate than discrete DTA and is ready to use for DTD implementation on patient cases.
7 Application of DTD on Patient cases

In this chapter, I implement both discrete and 3D continuous DTD on the 11 patient cases used in this thesis. The first section of this chapter establishes the linear correlation between discrete and continuous DTD on all patients, providing further assurance that the algorithms compute the same quantity. The second section presents DTD anatomical maps on patient cases for both discrete and continuous DTD, and the 3rd section draws a conclusion about the required spatial accuracy of a DVF used in dose mapping.

7.1 Discrete and 3D continuous DTA linear correlation

Figure 50, show scatter plots of the discrete DTD on the y-axis and the continuous DTD on the x-axis for patient P4P100 (Appendix VII contains the scatter plots for the rest of the patients Figure 95-Figure 104). The plots show that there is a linear correlation between the two codes with an average linear correlation coefficient of 0.99. To reduce voxel interpolation-related errors, all input dose distributions were computed at $2 \times 2 \times 2 \text{ mm}^3$ dose grid size.

The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \times \text{voxel size}$. Interpolation error occurs in adjacent voxels. In such cases, for a dose point in the test image, the corresponding dose point in the reference image is given by the continuous DTA as the dose point associated with the closest corner of the
reference voxel; however, for the discrete code, there is more than one potential location of the dose point candidate. If the interpolation occurs on the opposite corner to the real dose point, the maximum bound of the interpolation error will be given by \( \sqrt{2} \times \text{voxel size} \).

![Figure 50: scatter plot of discrete versus continuous DTD in mm for patient P4P100. The two red lines represent the maximum and minimum interpolation error which is equal to \( \sqrt{2} \times \text{voxel size} \).](image)

### 7.2 DTD application on patient cases

In previous work [58], we introduced the DTD concept and implemented it on one patient case to estimate the required spatial accuracy of a DVF. In this section, I implement both discrete and continuous DTD on 11 patient cases.

Figure 51 displays the color-wash maps on transverse slices of the dose distributions (a), the discrete (left) and continuous (right) DTD (b), and the DTDs difference
(c) for patient P4P100 (Appendix VIII contains the DTD color-wash maps for the rest of the patients Figure 105-Figure 114). For most patients, results agree with what we have reported in our previous study on one patient case. In dose gradients around the CTV, 1 to 7 mm DVF errors are permitted, and outside the treatment region DVF errors up to 10 mm are tolerated. Inside the CTV, up to 10 mm DVF errors are permitted depending on the uniformity of the dose distribution inside the CTV.

As for P4P104 [Figure 108], inside the CTV, 1-4 mm DVF error is permitted. In dose gradients around the CTV, 0.5 to 6 mm DVF errors are permitted, and outside the treatment region, DVF errors up to 10 mm are tolerated. The result for this patient is expected, since the dose distribution inside and around the CTV is not uniform. This confirms what we reported in the previous DTD work, in dose gradient regions the DVF has to be more accurate than in uniform dose regions.

Comparing both discrete and continuous DTD results, the 3D continuous code is faster than the discrete code. For a dose file of size 190x130x139 with dose grid size of $2 \times 2 \times 2 \ mm^3$ the 3D continuous code takes about a day. To lower errors due to dose interpolation the discrete code computations could take 2 to 3 days. The two color-wash maps looked similar and they were different in regions outside the patient surface and outside the radiation beams in low dose point values where the continuous code does not compute a DTD value (please note that for such regions a mask was applied on the discrete DTD files to make its values equivalent to the continuous code), inside the radiation beams the two codes gave identical results in sharp dose gradient regions and were different inside and around the CTV by an amount that ranges from 0.1 mm up to
\sqrt{2} \times \text{voxel size} \text{ which corresponds to the maximum interpolation error that can occur using the discrete DTD code.}
Figure 51: (a) Isodose lines on a single transverse slice of the computed dose for P4P100. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue), and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
7.3 Conclusion

The required spatial accuracy of a DVF was estimated for 11 lung cancer patients, using both discrete and continuous DTD codes. Results agreed with what we reported in our previous DTD work. For the one patient that showed big differences among all the dose mapping methods (MD-Anderson), the DTD map shows DVF accuracy is needed near the GTV. Thus, any small errors in the DVF reader could result in the large observed DME. The required spatial accuracy of a DVF depends on the uniformity of the dose distribution, is patient specific, and is greater than 10 mm in regions outside radiation fields. Both discrete and continuous showed similar DTD maps; however, continuous DTD followed the shape of the dose distribution, eliminating discretization dose error and is faster than the discrete DTD computations.

Finding the required spatial accuracy of a DVF has lots of benefits in the radiation therapy field. For DIR algorithms, it serves as a QA benchmark for these algorithms and helps to better improve their accuracy and speed. This thesis results show that a DVF does not have to be accurate in the whole image; thus, there is no need for the DIR algorithm to apply exhaustive computation to accurately generate DVF for the whole image. Including DTD results into 4D planning can further improve the accuracy of estimating the delivered dose to the patient. Since our results show that DTD distribution is patient-specific, visualizing DTD location maps on the patient anatomy before starting the dose mapping process can help in evaluating the location of acceptable and non-acceptable potential dose mapping error.
8 Thesis conclusion and future directions

This thesis work addresses errors that might occur when intra-fraction 4D dose calculations are performed for lung cancer treatment site. The work is divided into two specific aims. In specific aim one, a study of DME by comparing dose mapping algorithms: Pinnacle, Dtransform, and Tri-linear (with voxel subdivisions n= 1, 2 3) with respect to EMCM was done under two different conditions. The first part of specific aim one investigated the effect of choosing the planning target on DME, and the second part investigated the effect of changing the dose grid size on DME.

In specific aim two, a new concept called DTD was introduced to estimate the required spatial accuracy of a DVF used in dose mapping. A 3D continuous DTD algorithm was written and compared to discrete DTD code on phantom and patient cases.

8.1 Thesis findings

Specific aim one, part one study showed that, for breathing phase 50% on 11 patients, tissue density gradients were highest around the edge of the tumor, compared to the CTV, and the PTV edge voxels. Thus, treatment plans generated with margin equal to zero on the tumor might yield the highest DME. Under non-clinical conditions designed to maximize the DME clinical scenario and using a fine dose grid resolution of 2×2×2 mm³, treatment plans were generated directly on the tumor and 4D-dose distributions were generated for all patients using the above mentioned dose mapping algorithms.
For all patients, there was no clinical effect of DME on the MLD, lung V20, and Esophagus specified volume indices. Statistically, lung V20 and MLD showed significance for the entire dose mapping algorithms.

Two out of the 11 patients had D98 Pinnacle-DME of 4.4 (P4P103) and 1.2 (MD-Anderson) Gy. For P4P103, dose profiles showed that the differences were located in the penumbra region.

As for specific aim two, this thesis has the potential to improve DIR algorithms efficiency by introducing a DTD tool that estimates the required spatial accuracy of a DVF used for mapping the dose. Our results showed that a DVF does not need to be accurate in the whole image. DVF spatial accuracy for 11 patients is patient specific, and depends on uniformity of the dose distribution. In sharp dose gradient regions, DVF spatial accuracy of ~ 1 mm is needed, while 8 to 10 mm DVF accuracy can be tolerated before introducing any dose mapping errors inside the CTV (unless the dose inside the CTV is not uniform as in the P4P104 case) and > 10 mm in the rest of the dose grid areas.

The finding of this thesis work has the potential to increase the accuracy of 4D planning. This is achievable by using the ETM with mass sub-voxel mapping for a dose mapping algorithm. Although ETM with mass sub-voxel mapping results were similar to Pinnacle and Tri-linear with sub-voxel dose mapping algorithms, ETM accurately transports the energy events point by point on each of the breathing phases and deposits the energy in the reference breathing phase. The mass sub-voxel mapping implementation in ETM method increases the accuracy of ETM by mapping the mass of the breathing phases at almost a CT image resolution. ETM provides spatial energy distribution information, whereas only information about the average mapped energy is known for Dtransform.
Along with enforcing a 1 mm DVF spatial accuracy in dose gradient regions, an accurate estimation of the dose delivered to patient is achieved within 5% of the prescribed dose (uncertainty in MC calculations is < 2% and DTD criteria is set to 5% of the prescribed dose).

These thesis results also highlight the importance of choosing the planning target when designing a 4D plan. Results 0 showed that choosing the GTV as the planning target has the potential to cause high DME. Although having the GTV as the planning target is not clinically approved, current IGRT and SBRT plans aim to directly track the tumor dose and reduce margins around the tumor. For current clinical IMRT plans that utilize the use of margin around the tumor to reduce setup error, the results for two patients showed that using the PTV margin around the ITV (including tumor motion), will help in reducing the DME. The DTD results emphasize the importance of the uniformity of the dose around the target, since large DTDs, and thus tolerated spatial dose errors, are observed in regions of homogeneous doses around the GTV.

The final fruit of this thesis work is to provide more accurate and efficient DTA algorithm than a current in-house DTA algorithm, for that reason, based on an existing 2D DTA code, I wrote a 3D DTA algorithm that is free from discretization and interpolation error. The continuous 3D DTA is a multi-purpose algorithm that can compute a 3D gamma index and a 3D DTA index, which is the basic index to compute the DTD. The 3D continuous DTD algorithm is written, on dose phantom cases, is more accurate than the discrete DTD, and on patient cases, continuous DTD computations follow the shape of the dose distribution better than the discrete DTD code.
In conclusion, DME is patient specific and depends highly on the dose conformity level around the tumor. D98 RMS DME between ETM and DIM (Tri-linear) was reduced when a $2\times2\times2$ mm$^3$ planning dose grid size was used. Thus for patients with small tumor motion and deformation, at $2\times2\times2$ mm$^3$ planning dose grid size it does not matter which dose mapping algorithm to use for mapping the dose. Cases where there is large organ deformation we recommend using the EMCM algorithm even at $2\times2\times2$ mm$^3$. Spatial accuracy of the DVF is patient specific and is dependent on the uniformity of the dose distribution.

8.2 Future directions

The dose mapping study was done for intra-fraction 4D dose calculation for lung. It will be interesting to repeat the same study for inter-fraction 4D dose calculation for lung and for different treatment sites example head and neck, and abdominal cancers. Also, it is interesting to include different treatment modalities.

As for the DTD study, DTD calculation on more patients, different cancer sites and different modalities are interesting continuing studies.
9 References


10 Appendix I
A distance to dose difference tool for estimating the required spatial accuracy of a displacement vector field

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Purpose: To introduce a tool, termed distance to dose difference (DTD), which estimates the required spatial accuracy of displacement vector fields (DVF) used for mapping four dimensional dose values.

Methods: Dose mapping maps dose values from an irradiated geometry to a reference geometry. DVF errors result in dose being mapped from the wrong spatial location in the irradiated geometry, with a dose error equal to the dose difference between the error-free and sampled spatial locations. The DTD, defined as the distance to observe a given dose difference in the irradiated geometry, quantifies the permitted DVF error to ensure a prespecified desired dose mapping accuracy is achieved. To demonstrate the DTD, a treatment plan is generated with 5 mm internal target volume-to-planning target volume margin for an intensity modulated radiation therapy lung patient. The DTD is evaluated for mapping dose from the end of inhale image with a dose error tolerance of 3.30 Gy, which equals 3% of the 66 Gy prescription dose. The DTD is loaded into the treatment planning system to visualize positional dependencies of permissible DVF errors overlaid on the patient’s anatomy and DTD volume histograms are generated.

Results: DTD values vary with location in the patient anatomy. For the test case, DTD analysis indicates that accurate DVF (<1 mm) are required in high dose gradient regions while large DVF errors (>20 mm) are acceptable in low dose gradient regions. Within the clinical target volume (CTV), tolerated DVF uncertainties range from 1 to 12 mm, depending on location. Ninety percent of the CTV volume had DTD values less than 4 mm.

Conclusions: The DVF spatial accuracy required to meet a dose mapping accuracy tolerance depends on the spatial location within the dose distribution. For dose mapping, DVF accuracy must be highest in dose gradient regions, while less accurate DVF can be tolerated in uniform dose regions. The DTD tool provides a useful first estimate of DVF required spatial accuracy. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3572228]

1 INTRODUCTION

When delivering radiation therapy, patient anatomy changes between one fraction and another (interfraction) and even within the same fraction (intrafraction). As a result of patient anatomic changes, patient alignment variations, and beam delivery variations, the delivered dose distribution is time dependent. If unaccounted for, the uncertainties due to setup errors, random errors, tumor motion, tissue deformations, and beam delivery variations will lead to a difference between planned and delivered dose distributions, which in turn can degrade patient outcomes. Margins are used around the tumor to compensate for uncertainties due to setup errors and tumor motion; however, tracking tissue voxels from one instance of time to another is required to include the effect of these errors, motions, and tissue deformations on the treatment outcome of the irradiated anatomy.

Deformable image registration (DVF) to track movement of voxels from one image set to another. The DVF is used to track information between images such as image intensities, contours, or dose. Dose mapping is required to sum dose components delivered to different geometric instances of a patient's anatomy, such as from different phases of breathing in a four dimensional computed tomography (4DCT). Typically, for each point of the reference geometry, the DVF is utilized to find the corresponding point in the irradiated geometry, and then the dose in the reference geometry is assigned to be equal to that in the corresponding point in the irradiated geometry.

The accuracy of dose mapping, therefore, depends on the accuracy of the DVF used in the mapping process and on the local dose gradient in the irradiated geometry. For example, if a registration DVF error occurs in a uniform dose region [Fig. 1(a)], then the resultant dose error is small. Conversely, if a registration error occurs in a high dose gradient, such as in the penumbra region, [Fig. 1(b)] then resultant dose error can be large.

One can exploit this relationship between DVF accuracy and dose mapping accuracy to determine how large a DVF can be tolerated before it introduces a given dose error. For example, if the desired dose mapping accuracy is 2% of the local dose, then DVF errors are relevant only if the dose at an incorrectly mapped point is >2% different from the dose at the "correctly" mapped dose point. This suggests that a metric which provides an upper bound of allowable DVF uncertainty can be developed based upon a distance to dose difference (DTD) analysis, where the distance to a dose difference threshold in the irradiated geometry is evaluated.
Fig. 1. Illustration of the effect of DVF errors on dose mapping errors. On each panel, the green arrows are possible displacement vectors for mapping information from the irradiated image to the reference image. The red arrow represents the DVF error. In (a), the error occurs in a uniform dose region, hence the dose mapping error is minimal. In (b), the error occurs in a dose gradient region, resulting in a large dose mapping error.

The DTD concept is unique in that it does not require knowledge of the DVF. Instead, DTD indicates how large a DVF error can be before the DVF error could introduce a predetermined maximum tolerable dose mapping error. The DTD threshold is adaptable based on the desired evaluation; DTD can be for a given percentage of the local dose, given percentage of maximum dose, for any arbitrary absolute dose difference, or even to an absolute dose level.

This note introduces the DTD concept, demonstrates its use for mapping dose between two phases of a 4D lung plan, and compares the DTD with a method based on the gradient of the dose distribution.

II. METHOD AND MATERIALS

II.A. DTD algorithm

The DTD algorithm (Fig. 2) used in this work is developed using a technique similar to those used for distance to agreement (DTA) analysis. DTA utilizes two dose distributions, A and B, on a common coordinate system which are to be compared. For each dose value at a point in distribution A, the DTA is the shortest distance that must be traversed in B to have an equivalent dose value.14,17 This concept can be extended to a DTD concept. DTD utilizes a single dose distribution as input since the desire is to determine the minimum distance one must traverse in this dose distribution to observe a dose difference greater than the tolerance. For example, if the desired dose accuracy is 2% of the local dose, then beginning with dose distribution A, a dose distribution B' is created by multiplying the dose values in A by \((1 + \delta / 100)\) = 1.02. The DTA at each point between A and B' is then determined, producing DTA'. Similarly, a dose distribution B'' is created by multiplying the dose values in A by \((1 - \delta / 100)\) = 0.98 with the DTA at each point between A and B'' determining DTA''. At each point, the DTD to ensure a maximum of an n% local dose error will be the minimum of (DTA', DTA''). If one would like to know the DTD in terms of an absolute (Gy) dose value, e.g., \(\Delta D = 0.02\) Gy, then \(B'' = A + \Delta D\) and \(B' = A - \Delta D\), respectively, in the computation of DTA' and DTA''. Of course, one could directly write a DTD algorithm without directly utilizing DTA code; however, the simple method stated above enables use of established quality-assured algorithms for this study.

In this study, the DTD is based upon an in-house developed c++ DTA algorithm. The DTA algorithm progressively searches in shells of increasing radius (number of voxels) for...
the dose agreement point in matrix $B$ which surrounds the point of interest from matrix $A$. Internally, the DTA algorithm trilinearly interpolates the dose to a $1 \times 1 \times 1 \text{ mm}^3$ resolution in the search matrix to reduce errors inherent to the discrete voxel-based DTA algorithm used. Future implementations could be based on a more accurate or more efficient DTA algorithm, e.g., those described in Refs. 16–18.

II.B. DTD example

To demonstrate the utility of the DTD, intensity modulated radiation therapy (IMRT) lung treatment plan is generated using Pinnacle3 (Philips Medical Systems, Fitchburg, WI). The plan uses an internal target volume (ITV), generated from the union of the clinical target volume (CTV) on all breathing phases of a ten phase 4DCT (phase 0%–90%) plus a 0.5 cm ITV-planning target volume (PTV) margin. The treatment plan is generated on phase 0% (end of exhale). The minimum prescribed dose to the target is 66 Gy using direct machine parameters optimization, IMRT optimization with a $4 \times 4 \times 4 \text{ mm}^3$ dose grid resolution. The DTD is computed for both $4 \times 4 \times 4 \text{ mm}^3$ and $2 \times 2 \times 2 \text{ mm}^3$ dose grid resolutions based on the collapsed-cone dose algorithm dose values. The figures show the $4 \times 4 \times 4 \text{ mm}^3$ results unless otherwise noted.

Following planning, the DTD is determined for $n = 2\%$ of the local dose computed on phase 0% (DTD$_{2\%}$), and for $\Delta D = 1.32 \times$ (DTD$_{2\%}$) and 3.30 Gy (DTD$_{3\%}$), corresponding with 2% and 5% of the prescription dose. These values are chosen in accordance with suggested dose accuracy values listed in ICRU report 62.5

To visualize and analyze DTD, the externally computed DTD values are loaded into Pinnacle as a beam in a separate trial and the monitor units are adjusted so that dose values can be interpreted as distance values (in mm). This enables viewing of isoDTD lines on the patient’s anatomy and creation of DTD-volume histograms (DTDvhs) using pre-existing Pinnacle tools.

II.C. Comparison with dose gradient

An approach similar to the DTD is to evaluate the gradient of the 3D dose distribution, then divide the desired dose tolerance value by the dose gradient. This method is called TDG for tolerance divided by gradient. The 3D dose gradient is computed using the central difference method, yielding gradients in the $x$, $y$, and $z$ directions. TDG values are computed in two ways, one using the magnitude of the 3D dose gradient (TDG$^\text{mag}$) and the other using the maximum of the dose gradient $|\partial D/\partial x|$, $|\partial D/\partial y|$, $|\partial D/\partial z|$ in a given direction (TDG$^\text{max}$). The TDG method is compared with the DTD method by comparing color wash distributions, DTDvhs with TDGvhs, and plotting point-by-point DTD values with respect to TDG values.

III. RESULTS

Figure 3 shows the isodose lines on phase 0% for the IMRT plan overlay on a transverse slice of the patient's anatomy. This same transverse slice is used to show the DTD values in the later figures. Figure 4(a) shows the DTD$^\text{2\%}$ overlaid on this transverse slice. The maximum DTD$^\text{2\%}$ value observed inside the CTV is 6 mm, with values of 1–4 mm surrounding the CTV. Within the entire image, DTD$^\text{2\%}$ values as low as 0.1 mm are observed.

Figure 4(b) shows color wash isoDTDs for the DTD$^\text{1.32\%}$. Outside the irradiated region, the plan can tolerate up to 10 mm DVF errors. Inside the irradiated region, but outside the CTV in large dose gradient regions, DVF errors between 0.5 and 1 mm can be tolerated. Inside the CTV, the plan can tolerate up to 4 mm DVF error. Similarly, Fig. 4(c) shows color wash isoDTDs for the DTD$^\text{3\%}$. The DTD$^\text{3\%}$ differs from the DTD$^\text{1.32\%}$ demonstrating the variation of DTD with the required dose accuracy. Outside the irradiated region, the plan can tolerate up to 10 mm DVF errors. Inside the irradiated region, but outside the CTV in large dose gradient regions, DVF errors between 1 and 8 mm can be tolerated. Inside the CTV, the plan can tolerate up to 10 mm DVF errors.

These preliminary results suggest that accurate DVFs are not needed for the whole image for dose mapping purposes. For the two DTD distributions calculated, both results show that in high dose gradient regions, spatial dose or DVF accuracy requirements are tight, whereas inside the CTV or outside the treatment region both requirements can be relaxed and the plan can absorb more errors. While isoDTDvhs overlaid on the patient’s anatomy allow visual identification of areas which are tolerable or intolerable to DVF errors, to statistically interpret the spatial dose or DVF accuracy requirements, the DTD can be plotted as function of the volume of any structure. Figure 5 shows an example DTDvhs for the CTV structure for the 3.30 and 1.32 Gy dose difference DTD criteria. From these graphs, one can read out the DVF accuracy required as a function of the percentage volume of the structure. While not as useful as 3D visualization of the DTD, these DTDvhs enable simple statistical analysis of DTD properties.

DTDs calculated based on the $2 \times 2 \times 2 \text{ mm}^3$ dose grid resolution (not shown) look similar to the $4 \times 4 \times 4 \text{ mm}^3$ results shown in Fig. 4. DTD values should not vary
within the CTV for the different resolutions and due to limitations of the underlying DTA algorithm used.

The TDG_{30Gy} image for 3.30 Gy dose difference tolerance (TDG_{30Gy}) is shown in Fig. 6. Qualitatively, this image is similar to the DTD_{30Gy} (Fig. 4(c)) in dose gradient regions but differs in regions inside the CTV and outside the radiation beams where TDG_{30Gy} indicates larger tolerances of DVF or spatial dose errors from the DTD method. Figure 7 compares the point-by-point DTD_{30Gy} values with the TDG_{30Gy} values for dose points within the patient contour. The banding in the DTD values is due to the $1 \times 1 \times 1$ mm$^3$ resolution used within the DTA algorithm. Generally, TDG values are larger than DTD values for this case. Poor correlation between DTD_{30Gy} and TDG_{30Gy} values is observed, especially for large values. Points with large TDG_{30Gy} values yet small DTD_{30Gy} values are detected. The TDG is inversely proportional to the dose gradient. Because TDG_{30Gy} is significantly with dose grid resolution when the dose resolution is sufficient such that intermediate points can be trilinear interpolated with errors small compared with the size of the DTD criteria. For points within the patient contour, the average DTD values computed at the $4 \times 4 \times 4$ mm$^3$ and $2 \times 2 \times 2$ mm$^3$ resolutions differ by less than 0.05 mm, with a root-mean-square difference of 0.7 mm. Figure 5 shows that differences in the 3.3 Gy CTV DTDv values are less than 0.5 mm for the different dose matrix resolutions. The deviations are due to differences in dose values computed.
uses the magnitude of the gradient vector, which can have small components in one direction but large components in others, it can overestimate permissible spatial dose errors in low dose gradient region. In high dose gradient region, the TDG can overestimate or underestimate spatial dose errors depending on the curvature of the dose distribution.

TDGmax, which uses the maximum dose gradient, has similar poor correlation with the DTD (not shown). Overall, the TDG method is limited in its ability to evaluate acceptable DVF errors.

IV. DISCUSSION

The uncertainty in a deformable image registration algorithm will lead to uncertainty in the DVF generated. Several groups have been working on estimating the uncertainty in deformable image registration algorithms; however, little work has been done on finding the required spatial accuracy of a DVF. In this work, a simple algorithm is introduced to compute a distance to a dose difference to planar that can be related to how accurate the DVF used in dose mapping has to be before violating the specified dose accuracy tolerance. Current deformable image registration algorithms focus on creating an as-accurate-as-possible registration for an entire image or restrict over a given region of interest. The results of this work indicate that for dose mapping purposes, accurate registration is needed in high dose gradient regions, with less accuracy in uniform dose areas.

For simplicity, the example presented in this work evaluated the DTD between phases of a 4D lung treatment plan. Specifically, the DTD estimates the required DVF spatial accuracy needed to map dose delivered on the end of inhale breathing phase (phase 0%) to any of the other breathing phases. The tolerance values are selected as if the full treatment delivery occurred on the phase 0% image set. If dose delivery on multiple 4D breathing phases is considered, the sum of the DVF induced dose mapping errors (from the different mappings) would need to be less than the tolerance value. If the DTD dose error tolerance is equidistributed among the breathing phases, the dose delivered and DTD threshold values change by the same fraction, resulting in the same DTD for the phase 0% to phase % mappings as given above. Alternatively, the DTD dose error tolerance could be unequally distributed among the different image sets, while still requiring that the total dose error induced is less than the threshold. This complex analysis is left for further study.

The example presented in this paper utilized DTD tolerance values with respect to target dose values. However, the DTD concept is general and DTDs can be computed to arbitrary, even region of interest specific tolerances. For example, for critical structures, an appropriate tolerance could be the maximum tolerated dose.

The DTD tool provides qualitative utilities when interfaced with a treatment planning system; DTD can be visualized as iso/DTD lines/color washes that provide the planner with the ability to see geographical maps of tolerated and untolerated DVF errors before using a specified DVF with a given uncertainty for dose mapping. DTD-volume histograms can provide volume-based statistical error analysis for targets, organs at risk, or arbitrary regions of interest in an image.

The DTD tool is not limited to estimating the spatial accuracy of a DVF. For a given dose difference tolerance (absolute or %), one can determine the distance error that can be tolerated before violating the specified dose accuracy. For a CTV, the DTD can be used as a first estimate of how large a setup error can be before introducing a clinically significant dose error. Similarly, knowledge of the maximum tolerated setup error can be used in plan evaluation, possibly affecting CTV-to-PTV or organ at risk-to-planning risk volume (PRV) planning margins.

V. CONCLUSIONS

This work introduces a new method which estimates how large a DVF error can be tolerated before introducing a potentially clinically significant error in the dose mapping processes. The required DVF spatial accuracy will depend on the particular dose distribution. For dose mapping, DVF accuracy must be highest in dose gradient regions, while less accurate DVFs can be tolerated in uniform dose regions. The DTD tool can be used as a first estimate of DVF required spatial accuracy and can be applied to other areas when the distance to a dose difference tolerance is required to be known.

ACKNOWLEDGMENTS

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11 Appendix II
Figure 52: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P101. The yellow vectors represent the DVFs (0->N%).
Figure 53: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P102. The yellow vectors represent the DVFs (0->N%).
Figure 54: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P103. The yellow vectors represent the DVFs (0->N%).
Figure 55: Transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P104. The yellow vectors represent the DVFs (0->N%).
Figure 56: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%→0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0→N%)(green) and the manual GTV on phase 0% for patient P4P105. The yellow vectors represent the DVFs (0→N%).
Figure 57: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P106. The yellow vectors represent the DVFs (0->N%).
Figure 58: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P107. The yellow vectors represent the DVFs (0->N%).
Figure 59: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P110. The yellow vectors represent the DVFs (0->N%).
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**Data Set:** P4\P114*5300*100003

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**ROI Name:** Tumor_c00 (PIDVTf10) (Demons)

**Data Set:** P4\P114*5300*100003

**ROI Type:** ORGAN

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**Data Set:** P4\P114*5300*100003

**ROI Type:** ORGAN

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**ROI Name:** Tumor_c00 (PIDVTf10) (Demons)

**Data Set:** P4\P114*5300*100003

**ROI Type:** ORGAN

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Figure 60: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient P4P114. The yellow vectors represent the DVFs (0->N%).
Figure 61: transverse, sagittal, and coronal views of the planning phase (0%) showing the generated GTV0 (PIDVF N%->0) on phase N% mapped back to phase 0% using the Pinnacle DVFs (0->N%)(green) and the manual GTV on phase 0% for patient MD-Anderson. The yellow vectors represent the DVFs (0->N%).
Figure 62: Patient P100 complementary cumulative distribution sum of the frequency of the PTV, CTV, and tumor edge voxels on the y-axis versus phase 50 % image gradient on the edge voxels of the PTV, CTV, and tumor curves.
Figure 63: Patient P101 complementary cumulative distribution sum of the frequency of the PTV, CTV, and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV, and tumor curves.

Figure 64: Patient P102 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 65: Patient P103 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50 % image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 66: Patient P104 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50 % image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 67: Patient P105 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50 % image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 68: Patient P106 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 69: Patient P107 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 70: Patient P110 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 71: Patient P114 complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50% image gradient on the edge voxels of the PTV, CTV and tumor curves.
Figure 72: Patient MD-Anderson complementary cumulative distribution sum of the frequency of the PTV, CTV and tumor edge voxels on the y-axis versus phase 50 % image gradient on the edge voxels of the PTV, CTV and tumor curves.
13 Appendix IV

Table 14: 4D-DVHs of the accumulated dose on the reference phase for each patient on the left. On the right is the difference in DVH indices among dose mapping methods with respect to EMCM: tumor D98, D50, mean lung dose, dose to 10 or 1% of the cord in cGy and percentage difference in volume indices for lung, Esophagus and normal tissue.

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163
P4P110

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<td>-8</td>
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<tr>
<td>Heart V40 %</td>
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P4P14

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<td>MLD cGy</td>
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<td>0.04</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.15</td>
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14 Appendix V

Figure 73: P4P100 coronal slices showing the location of maximum absolute DME for Dtransform on the left, Tri-linear with n =3 in the middle, and Pinnacle on the right. Shown in red color-wash is the tumor. The maximum absolute DME point was located outside the patient.

Figure 74: P4P101 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle, and Dtransform on the right. Shown in red color-wash is the tumor.
Figure 75: P4P102 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle, and Dtransform on the right. Shown in red color wash is the tumor.

Figure 76: P4P103 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.
Figure 77: P4P104 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.

Figure 78: P4P105 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor. The maximum absolute DME point was located outside the patient surface.

Figure 79: P4P106 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor. The maximum absolute DME point was located on the patient surface for Pinnacle and tri-linear, and outside the radiation field for Dtransform.
Figure 80: P4P107 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with \( n = 3 \) in the middle and Dtransform (sagital) on the right. Shown in red color wash is the tumor. The maximum absolute DME point was located inside the radiation field but away from the tumor.

Figure 81: P4P110 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with \( n = 3 \) in the middle and Dtransform on the right. Shown in red color wash is the tumor. The maximum absolute DME point was located outside the patient surface.
Figure 82: P4P114 coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor. The maximum absolute DME point was located outside the patient surface.

Figure 83: MD Anderson coronal slices showing the location of maximum absolute DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor. The maximum DME point was located outside the patient surface.
Figure 84: P4P100 coronal slices showing the location of maximum DME for Dtransform on the left, Tri-linear with \( n = 3 \) in the middle, and Pinnacle on the right. Shown in blue color-wash is the tumor.

Figure 85: P4P101 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with \( n = 3 \) in the middle, and Dtransform on the right. Shown in red color-wash is the tumor.
Figure 86. P4P102 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with \( n = 3 \) in the middle, and Dtransform on the right. Shown in red color wash is the tumor.

Figure 87: P4P103 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with \( n = 3 \) in the middle and Dtransform on the right. Shown in red color wash is the tumor.
Figure 88: P4P104 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.

Figure 89: P4P105 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.

Figure 90: P4P106 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.
Figure 91: P4P107 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform (sagital) on the right. Shown in red color wash is the tumor.

Figure 92: P4P110 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.
Figure 93: P4P114 coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.

Figure 94: MD Anderson coronal slices showing the location of maximum DME for Pinnacle on the left, Tri-linear with n =3 in the middle and Dtransform on the right. Shown in red color wash is the tumor.
15 Appendix VI

Table 15: 4D-DVHs of the accumulated dose on the reference phase for each patient using $4 \times 4 \times 4 \text{ mm}^3$ and $2 \times 2 \times 2 \text{ mm}^3$ on the left. On the right are tables for each patient with data that corresponds to the absolute difference in OAR 4D-DVH volume indices with respect to EMCM $2 \times 2 \times 2 \text{ mm}^3$ for both dose grid sizes for EMCM, N1, N3, and Pinnacle dose mapping algorithms.

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<td>0.1</td>
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<tr>
<td>Heart(%) $V_{40GY}$</td>
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<tr>
<td>Lung(%) $V_{20GY}$</td>
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**Volume %**

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**Volume %**

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**Volume %**

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**Diagrams:**
- One diagram shows the fractional volume versus dose for different tissues and structures.
- Another diagram displays the same data for another set of conditions.
Table 16: 4D-DVHs of the accumulated dose on the reference phase for each patient for the 4 mm dose grid size on the left. On the right is the difference in DVH indices among dose mapping methods with respect to EMCM: tumor D98, D50, mean lung dose, dose to 10 or 1% of the cord in cGy and percentage difference in volume indices for lung, Esophagus and normal tissue.

![Graph](image)

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### P4P103

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Figure 95: scatter plot of discrete versus continuous DTD in mm for patient P4P101. The two red lines represent the maximum and minimum interpolation error which is equal to \( \sqrt{2 \cdot \text{voxel size}} \).
Figure 96: scatter plot of discrete versus continuous DTD in mm for patient P4P102. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \times \text{voxel size.}$
Figure 97: scatter plot of discrete versus continuous DTD in mm for patient P4P103. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2^*\text{voxel size}}$. 
Figure 98: scatter plot of discrete versus continuous DTD in mm for patient P4P104. The two red lines represent the maximum and minimum interpolation error which is equal to \( \sqrt{2 \cdot \text{voxel size}} \).
Figure 99: scatter plot of discrete versus continuous DTD in mm for patient P4P105. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2^*\text{voxel size}}$. 
Figure 100: scatter plot of discrete versus continuous DTD in mm for patient P4P106. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \times $voxel size.
Figure 101: scatter plot of discrete versus continuous DTD in mm for patient P4P107. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \times$ voxel size.
Figure 102: scatter plot of discrete versus continuous DTD in mm for patient P4P110. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \cdot \text{voxel size.}$
Figure 103: scatter plot of discrete versus continuous DTD in mm for patient P4P114. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2}\text{voxel size}$. 
Figure 104: scatter plot of discrete versus continuous DTD in mm for patient MD-Anderson. The two red lines represent the maximum and minimum interpolation error which is equal to $\sqrt{2} \times $voxel size.
17 Appendix VIII

(a)

(b)
Figure 105: (a) Isodose lines on a single transverse slice of the computed dose for P4P101. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 106: (a) Isodose lines on a single transverse slice of the computed dose for P4P102. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 107: (a) Isodose lines on a single transverse slice of the computed dose for P4P103. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 108: (a) Isodose lines on a single transverse slice of the computed dose for P4P104. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 109: (a) Isodose lines on a single transverse slice of the computed dose for P4P105. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 110: (a) Isodose lines on a single transverse slice of the computed dose for P4P106. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 111: (a) Isodose lines on a single transverse slice of the computed dose for P4P107. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 112: (a) Isodose lines on a single transverse slice of the computed dose for P4P110. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 113: (a) Isodose lines on a single transverse slice of the computed dose for P4P114. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.
Figure 114: (a) Isodose lines on a single transverse slice of the computed dose for MD-Anderson. The minimum prescribed dose (66 Gy) is indicated in blue. Structures in color wash are CTV (purple), esophagus PRV (blue) and cord PRV (orange). (b) Color wash of the discrete (on the left) and 3D continuous (on the right) DTD3.30Gy values. (c) Color wash of the difference between discrete and continuous DTDs. Each color wash values represent the lower bound of the value, e.g. 1 mm corresponds to DTDs ranging from 1.0 to 2.0 mm.