Volumetric Cine Imaging for On-board Target Localization in Radiation Therapy

by

Wendy Beth Harris

Graduate Program in Medical Physics
Duke University

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Approved:

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Lei Ren, Supervisor

___________________________
Fang-Fang Yin, Supervisor

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Bastiaan Driehuys, Chair

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Jing Cai

___________________________
Zheng (Jim) Chang

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Brian Czito

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Medical Physics Graduate Program in the Graduate School of Duke University

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ABSTRACT

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Abstract

Accurate target localization is critical for liver and lung cancers due to uncertainties caused by respiratory motions. On-board four-dimensional (4D) or real-time verification of the tumor before and during Stereotactic Body Radiation Therapy (SBRT) is necessary because SBRT uses high fractional doses, tight Planning Target Volume (PTV) margins and a long treatment time. Current imaging of moving targets for on-board localization cannot image full volumetric information in real-time. The purposes of this dissertation research are to do the following. (1) Develop a real-time quasi-cine CBCT reconstruction method for on-board CBCT-guided target verification; (2) Develop a volumetric cine MRI (VC-MRI) technique for on-board MRI-guided target verification using an MRI-guided radiotherapy machine; (3) Develop an on-board 4D MRI technique for on-board MRI-guided target verification using kV projections from a conventional linear accelerator (LINAC); (4) Accelerate VC-MRI through undersampling acquisition while maintaining image quality; and (5) Improve geometric accuracy of VC-MRI through novel undersampling acquisition and deformation models.

A technique for 4D CBCT estimation was previously developed using a deformation field map (DFM)-based strategy. In the previous method, each phase of the 4D CBCT was generated by deforming a prior CT volume acquired during simulation. The DFM was solved by a global motion model (GMM) extracted by a global Principal
Component Analysis (PCA) from prior 4D-CT and free-form deformation (FD) technique, using a data fidelity constraint. However, this technique has limitations in both reconstruction time (~5 minutes) and accuracy. In the new proposed study of this dissertation, a quasi-cine CBCT estimation technique was developed to address these issues for real-time application. Specifically, a new structural PCA method was developed to build a structural motion model (SMM) instead of GMM by accounting for potential relative motion pattern changes between different anatomical structures from simulation to treatment. The motion model extracted from planning 4D CT was divided into two structures: tumor and body excluding tumor, and the parameters of both structures were optimized together. Weighted free-form deformation (WFD) was employed afterwards to introduce flexibility in adjusting the weightings of different structures in the data fidelity constraint based on clinical interests. As such, the localization accuracy could be substantially improved with extremely limited angle kV projections. The technique was evaluated by simulating a 30 mm diameter lesion in a computerized patient model (XCAT) with various anatomical and respiratory changes from planning 4D CT to on-board volume. The estimation accuracy was evaluated by the volume percent difference (VPD)/center-of-mass-shift (COMS) between lesions in the estimated and "ground-truth" on-board quasi-cine CBCT. Different on-board projection acquisition scenarios and projection noise levels were simulated to investigate their
effects on the estimation accuracy. The method was also evaluated against three lung patients.

The SMM-WFD method achieved substantially better accuracy than the GMM-FD method for CBCT estimation using extremely small scan angles or projections. Using orthogonal 15° scanning angles, the VPD/COMS were 3.47 ± 2.94% and 0.23 ± 0.22 mm for SMM-WFD and 25.23 ± 19.01% and 2.58 ± 2.54 mm for GMM-FD among all eight XCAT scenarios. Compared to GMM-FD, SMM-WFD was more robust against reduction of the scanning angles down to orthogonal 10° with VPD/COMS of 6.21 ± 5.61% and 0.39 ± 0.49 mm, and more robust against reduction of projection numbers down to only 8 projections in total for both orthogonal-view 30° and orthogonal-view 15° scan angles. SMM-WFD method was also more robust than the GMM-FD method against increasing levels of noise in the projection images. Additionally, the SMM-WFD technique provided better tumor estimation for all three lung patients compared to the GMM-FD technique.

The first technique developed in this dissertation showed that compared to the GMM-FD technique, the SMM-WFD technique can substantially improve the CBCT estimation accuracy using extremely small scan angles and low number of projections to provide fast low dose 4D target verification.

The next section of the dissertation describes ways in which volumetric cine MRI (VC-MRI) was developed for MRI-guided radiation therapy. Currently, there are no
ways to image real-time MRI in three-dimensions (3D) for on-board MRI-guided radiotherapy. In the first subsection of the second section of this dissertation, a novel technique was developed to generate, for the first time, real-time 3D VC-MRI using patient prior images, motion modeling and on-board two-dimensional (2D) cine MRI.

One phase of a 4D MRI acquired during patient simulation is used as patient prior images. Three major respiratory deformation patterns of the patient are extracted from 4D MRI based on PCA. The on-board VC-MRI at any instant is considered as a deformation of the prior MRI. The deformation field is represented as a linear combination of the 3 major deformation patterns. The coefficients of the deformation patterns are solved by the data fidelity constraint using the acquired on-board single 2D cine MRI. The method was evaluated using both XCAT simulation of lung cancer patients and MRI data from 4 real liver cancer patients. The accuracy of the estimated VC-MRI was quantitatively evaluated using VPD, COMS, and target tracking errors. Effects of acquisition orientation, region-of-interest (ROI) selection, patient breathing pattern change, and noise on the estimation accuracy were also evaluated.

Image subtraction of ground-truth with estimated on-board VC-MRI showed fewer differences than image subtraction of ground-truth with prior image. Agreement between normalized profiles in the estimated and ground-truth VC-MRI was achieved with less than 6% error for both XCAT and patient data. Among all XCAT scenarios, the VPD between ground-truth and estimated lesion volumes was, on average, $8.43 \pm 1.52\%$.
and the COMS was, on average, 0.93 ± 0.58 mm across all time steps for estimation based on the ROI region in the sagittal cine images. Matching to ROI in the sagittal view achieved better accuracy when there was substantial breathing pattern change. The technique was robust against noise levels up to Signal-to-Noise Ratio (SNR) = 20. For patient data, average tracking errors were less than 2 mm in all directions for all patients. The feasibility of generating real-time VC-MRI for on-board localization of moving targets was demonstrated.

Next, a technique was developed to explore the feasibility of using an on-board kV imaging system and patient prior MRI knowledge to generate on-board quasi-cine volumetric MRI for target localization. Very few clinics have MRI-guided radiotherapy units, but most clinics have kV imaging capabilities with a conventional LINAC. The technique developed in this section of the dissertation aims to utilize conventional LINAC imaging capabilities, along with prior patient 4D MRI to estimate on-board 4D MRI for MRI-guided radiotherapy. Prior 4D MRI volumes were separated into end-of-expiration (EOE) phase (MRI\textsubscript{prior}) and all other phases. MRI\textsubscript{prior} was used to generate a synthetic CT at EOE phase (sCT\textsubscript{prior}). On-board quasi-cine 3D or 4D MRI at each respiratory phase was considered a deformation of MRI\textsubscript{prior}. The Deformation Field Map (DFM) was estimated by matching Digitally Reconstructed Radiographs (DRRs) of the deformed sCT\textsubscript{prior} to on-board kV projections using a MM-FD deformation optimization algorithm. The on-board 4D MRI method was evaluated using both XCAT simulation

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and real patient data. The accuracy of the estimated MRI was quantitatively evaluated using VPD, Volume Dice Coefficient (VDC) and COMS. Effects of scan angle and number of projections were also evaluated.

In the XCAT study, VPD/VDC/COMS among all XCAT scenarios were 10.16±1.31%/0.95±0.01/0.88±0.15mm using orthogonal-view 30° scan angles with 102 projections. The on-board 4D MRI method was robust against various scan angles and projection numbers evaluated. In the patient study, estimated on-board 4D MRI was generated successfully when compared to the ‘reference on-board 4D MRI’ for the liver patient case. Preliminary results for this novel technique demonstrated the potential for MRI-based image guidance for liver SBRT using only a kV imaging system on a conventional LINAC.

The last section of the dissertation aims to accelerate the VC-MRI technique developed and improve the estimation accuracy by using novel undersampling and deformation models. VC-MRI was accelerated by using undersampled 2D cine MRI to provide real-time 3D guidance. Undersampled Cartesian and radial k-space acquisition strategies were investigated. The effects of k-space sampling percentage (SP) and distribution, tumor sizes and noise on the VC-MRI estimation were studied. The accelerated VC-MRI estimation was evaluated using XCAT simulation of lung cancer patients and data from liver cancer patients. VPD and COMS of the tumor volumes and tumor tracking errors were calculated.
For XCAT, VPD/COMS were $11.93 \pm 2.37\%/0.90 \pm 0.27\,\text{mm}$ and $11.53 \pm 1.47\%/0.85 \pm 0.20\,\text{mm}$ among all scenarios with Cartesian sampling (SP = 10%) and radial sampling (21 spokes, SP = 5.2%), respectively. When tumor size decreased, higher sampling rate achieved more accurate VC-MRI than lower sampling rate. VC-MRI was robust against noise levels up to SNR = 20. For patient data, the tumor tracking errors in superior-inferior, anterior-posterior and lateral directions were $0.46 \pm 0.20\,\text{mm}$, $0.56 \pm 0.17\,\text{mm}$ and $0.23 \pm 0.16\,\text{mm}$, respectively, for Cartesian-based sampling with SP = 20% and $0.60 \pm 0.19\,\text{mm}$, $0.56 \pm 0.22\,\text{mm}$ and $0.42 \pm 0.15\,\text{mm}$, respectively, for radial-based sampling with SP = 8% (32 spokes).

Results from this method showed that VC-MRI could be accelerated from a single undersampled on-board 2D cine MRI. Phantom and patient studies showed that the temporal resolution of VC-MRI can potentially be improved by 5-10 times using a 2D cine image acquired with 10-20% k-space sampling.

Lastly, VC-MRI accuracy was improved by using multi-slice undersampled cine images, patient prior 4D MRI, motion modeling and free-form deformation. In this study, free-form deformation (FD) was introduced to correct for errors in the MM when large anatomical changes exist. Multiple-slice undersampled on-board 2D-cine images were used by reconstructing 10% of total k-space using a novel k-t SLR reconstruction method, which uses both the spatial and temporal resolution of the k-space data to reconstruct the 2D cine MRIs. The method was evaluated using XCAT simulation of
lung cancer patients with various anatomical and respirational changes from prior 4D MRI to onboard volume. The accuracy was evaluated using VPD, VDC and COMS of the estimated tumor volume. Effects of ROI selection, 2D-cine slice orientation, slice number and slice location on the estimation accuracy were evaluated.

VC-MRI estimated using 10 undersampled sagittal 2D cine MRIs achieved VPD/VDC/COMS of 9.77±3.71%/0.95±0.02/0.75±0.26mm among all scenarios based on estimation with ROI MM and ROI FD. The FD optimization improved estimation significantly for scenarios with anatomical changes. Using ROI FD achieved better estimation than global FD. Changing the multi-slice orientation to axial, coronal, and axial/sagittal orthogonal reduced the accuracy of VC-MRI. Estimation using slices sampled uniformly through the tumor achieved better accuracy than using slices sampled non-uniformly.

In conclusion, the work presented in his dissertation builds upon previous research and develops novel solutions for generating real-time volumetric cine images for both CBCT and MRI. The completed research dissertation presents the following: (1) develops a quasi-real-time cine CBCT reconstruction method using structural PCA and weighted free-form deformation, (2) develops a VC-MRI technique using motion modeling and single slice 2D cine acquisition, (3) develops an on-board 4D-MRI technique using limited on-board kV projections from a conventional LINAC and deformation models, (4) accelerates VC-MRI through undersampling acquisition while
maintaining image quality, and (5) improve geometric accuracy of VC-MRI through novel undersampling acquisition and deformation models.
Dedication

This work is dedicated to the people who have supported me and have positively influenced me throughout my journey. To my parents, Jill and Bruce Harris, for being great role models for me to look up to, and for always supporting me and encouraging me to pursue this degree. And to my brother, Dave Harris, for always being loving, supportive and genuinely interested in all that I do.
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List of Abbreviations

% Percent

2D Two-Dimensional

3D Three-Dimensional

4D Four-Dimensional

AP Anterior-Posterior

CBCT Cone-Beam Computed Tomography

cm Centi-meter

COMS Center of Mass Shift

CP Central Percentage

CT Computed Tomography

DFM Deformation Field Map

DRR Digitally Reconstructed Radiograph

DTS Digital Tomosynthesis

EOE End-of-Expiration

FD Free-form Deformation

FDK Feldkamp-Davis-Kress

FX Fraction

GPU Graphic Processing Unit

GTV Gross Tumor Volume
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>Gy</td>
<td>Gray; unit of radiation dose (1 Joule/kilogram)</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield Unit</td>
</tr>
<tr>
<td>IGRT</td>
<td>Image Guided Radiation Therapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>ITV</td>
<td>Internal Target Volume</td>
</tr>
<tr>
<td>keV</td>
<td>Kilo-voltage, for monochromatic energy</td>
</tr>
<tr>
<td>kV</td>
<td>Kilo-voltage</td>
</tr>
<tr>
<td>kVp</td>
<td>Peak Kilo-voltage</td>
</tr>
<tr>
<td>LINAC</td>
<td>Linear Accelerator</td>
</tr>
<tr>
<td>LAT</td>
<td>Lateral</td>
</tr>
<tr>
<td>MM</td>
<td>Motion Modeling</td>
</tr>
<tr>
<td>mm</td>
<td>milli-meter</td>
</tr>
<tr>
<td>MM-FD</td>
<td>Motion Modeling and Free-form Deformation</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MV</td>
<td>Mega-voltage</td>
</tr>
<tr>
<td>NCC</td>
<td>Normalized Cross Correlation</td>
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<tr>
<td>NSCLC</td>
<td>Non-small Cell Lung Cancer</td>
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<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>proj</td>
<td>Projection</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
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<td>ROIFD</td>
<td>Region of Interest-Free-form Deformation</td>
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<tr>
<td>ROIMM</td>
<td>Region of Interest-Motion Modeling</td>
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<tr>
<td>S</td>
<td>Seconds</td>
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<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiation Therapy</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-Inferior</td>
</tr>
<tr>
<td>SMM</td>
<td>Structural Motion Modeling</td>
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<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
</tr>
<tr>
<td>SP</td>
<td>Sampling Percentage</td>
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<tr>
<td>SPECT</td>
<td>Single-photon Emission Computed Tomography</td>
</tr>
<tr>
<td>TGV</td>
<td>Total Generalized Variation</td>
</tr>
<tr>
<td>TV</td>
<td>Total Variation</td>
</tr>
<tr>
<td>VC-MRI</td>
<td>Volumetric Cine MRI</td>
</tr>
<tr>
<td>VDC</td>
<td>Volume Dice Coefficient</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
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<tr>
<td>VPD</td>
<td>Volume Percent Different</td>
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<tr>
<td>WFD</td>
<td>Weighted Free-form Deformation</td>
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<td>XCAT</td>
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1. Introduction

The goal of radiation therapy is to deliver a high amount of radiation to the target region and as little amount of radiation as possible to the surrounding healthy tissues and organs. Target control and normal tissue complication probabilities are highly correlated to target localization accuracy in radiation therapy [1]. Accurate localization of liver and lung cancers in radiation therapy is challenging due to uncertainties caused by respiratory motions of the target. Stereotactic body radiation therapy (SBRT) is becoming an emerging and effective treatment paradigm to treat early stage liver cancer and non-small cell lung cancer (NSCLC) patients with very promising early clinical outcomes [2-6]. Currently, however, no imaging technique is capable of localizing the 3D target volume in real-time to ensure precise delivery of SBRT. This poses a major challenge to further improving local control and reducing the toxicities of SBRT. This dissertation aims to do the following. (1) Develop a real-time quasi-cine CBCT reconstruction method for on-board CBCT-guided target verification for lung radiotherapy; (2) Develop a volumetric cine MRI (VC-MRI) technique for on-board MRI-guided inter- and intra-fraction target verification of liver and lung radiotherapy using an MRI-guided radiotherapy machine; (3) Develop an on-board 4D MRI technique for on-board MRI-guided target verification using kV projections from a conventional linear accelerator (LINAC); (4) Accelerate VC-MRI through undersampling acquisition while
maintain image quality; and (5) Improve geometric accuracy of VC-MRI through novel undersampling acquisition and deformation models.

2. Background

2.1 Clinical Significance

The overall workflow of radiation therapy includes three main steps: 1) immobilization and imaging for patient simulation and volume delineation, 2) treatment planning design and optimization, and 3) on-board target localization and treatment delivery. The imaging process for patient simulation consists of acquiring CT images of patients immobilized in the treatment position. In addition to CT images, MRI, PET and/or SPECT images may also be acquired to provide additional anatomical or functional information for target delineation. In the treatment planning process, the target volume is contoured based on the images acquired in the simulation, and treatment beams are placed to deliver a specified prescription dose to the target while sparing the surrounding healthy tissues within the tolerances. In treatment delivery, precision of the target localization determines the accuracy of the dose delivery. Errors can occur, which can lead to radiation under-dose to the tumor and over-dose to the surrounding healthy tissues. Such errors may be caused by a number of factors such as positioning errors, respiratory motion or anatomical changes from the patient. Advanced radiotherapy treatment techniques such as intensity-modulated radiation therapy (IMRT) [7] and volumetric modulated arc therapy (VMAT) produce a highly
conformal radiation dose to cover the planning target volume (PTV) with steep dose gradients outside the PTV to spare the surrounding healthy tissues. Because of the high dose conformity, target misalignments may cause more under-dose to the tumor and high over-dose to the healthy tissues.

Accurate target localization is especially critical for SBRT treatments [8-13] for the following reasons. First, SBRT uses PTV margins as small as 5-10 mm for liver and 3-5 mm for lung treatments to reduce the toxicity to nearby healthy tissues [3, 4]. However, small margins also make the treatment more susceptible to target localization errors caused by both inter-and intra-fraction motions. Secondly, SBRT delivers a much higher fractional dose with fewer fractions compared to conventional treatments. Liver SBRT typically delivers 10-20 Gy/fx with 3-5 fractions [4, 14-17] while lung SBRT delivers 10-34 Gy/fx with 1-5 fractions [18, 19]. Treatment errors in a single fraction can lead to significant under dose to the target or over dose to healthy tissues for the entire treatment course. Lastly, the treatment time for SBRT varies from 30 to 60 minutes, depending on the motion management and delivery techniques. Studies show that patient motion increased with treatment time to as much as 1 cm with CBCT [20], leading to more localization errors in SBRT.

Image guided radiation therapy (IGRT) has been introduced to use on-board imaging techniques to improve the precision of the radiation delivery [8]. Various 2D and 3D X-ray based and MRI techniques have been developed for on-board image
guidance. Although proven to be effective for many treatment sites, these techniques are not sufficient for localizing tumors with respiratory motions, such as lung and liver cancers, due to the lack of motion information in the images. Developments of 3D volumetric cine imaging techniques are warranted to truly localize the 3D target volume in real time to minimize or even eliminate the target localization errors both before and during the treatment delivery.

2.2 Previous Developments in On-board Imaging Techniques

2.2.1. X-ray Based Imaging Techniques

2.2.1.1. 2D X-ray Based Imaging Techniques

On-board 2D KV or MV images can be acquired using an on-board flat panel detector or electronic portal imaging detector for target verification during radiotherapy. However, the major limitation of 2D imaging is that it does not provide full volumetric information of the patient. As a result, the accuracy of the 2D target localization techniques is limited by the availability of traceable features and low contrast of the target due to overlaying high contrast features (e.g. spine, chest wall), as reported by Rottmann et al. [21, 22]. This limitation is even more severe for the small tumors treated in SBRT [22]. Implanted markers in the tumor, as used in some commercial systems [23, 24] can improve the localization accuracy [25, 26] but this approach may not be applicable for all patients as it requires the invasive procedure of marker implantation. In addition, the locations of the markers may not accurately reflect the location of the
tumor because of soft tissue deformation, tumor size change and marker migration [27]. Willoughby et al. reported that the distance from the center of the fiducials to the center of the lung GTV changed up to 5mm due to asymmetric tumor deformation and shrinkage [24]. Marker migration can further worsen the problem to cause even larger localization errors. Essentially, all of the limitations of 2D imaging mentioned above are due to the missing of volumetric information in the 2D images. Only volumetric imaging can provide absolute verification of the target volume.

2.2.1.2. 3D/4D X-ray Based Imaging Techniques

For volumetric imaging, on-board 3D/4D tomographic imaging techniques such as 3D/4D DTS [28-30] and 3D/4D CBCT [31-36] have been investigated recently for moving target verification. Both 4D DTS and 4D CBCT use retrospectively respiratory-phase sorted cone-beam projections to reconstruct respiratory-phase-resolved volumetric images through the Feldkamp-Davis-Kress (FDK) algorithm [37]. 4D DTS are generated by using limited angle projections, and the 4D CBCT are generated by using full angle (200° using full fan or 306° using half fan) projections. The 4D aspect of these imaging techniques enables the trajectory of moving targets to be captured, which can lead to better alignment of the target volume and delineation.

4D DTS has a shorter scan time, lower imaging dose and better mechanical clearance compared to 4D CBCT, and shows promising results for target localization [28, 29]. But, 4D DTS has poor resolution along the plane-to-plane direction with no full
volumetric information due to the insufficient sampling [38]. The poor resolution and lack of volumetric information leads to severe tumor and healthy tissue distortions, which makes it impossible to achieve accurate target localization and delineation.

4D CBCT provides excellent volumetric images for both target localization and delineation. However, 4D CBCT reconstructed by the FDK algorithm requires full 200° or 360° projections with a high number of projections (~10^3), requiring long acquisition time and generating high imaging dose, which limits its clinical application. Many reconstruction methods have been proposed as alternatives to the traditional FDK algorithm, which utilize sparsely sampled and/or limited angle projections [39-46]. These methods use motion-modeling (MM) to estimate the 4D CBCT images from prior planning 4D CT images. The on-board 4D CBCT images are estimated by deforming the prior CT images using a deformation field map (DFM). The goal of these methods is to solve for the DFM to best estimate the on-board CBCT based on a data fidelity constraint, which requires the digital reconstructed radiographs (DRRs) of the deformed CT volumes to match with the on-board acquired projections. Because these methods utilize prior 4D planning CT information, only limited angle on-board projections are needed to reconstruct the 4D CBCT, which reduces the scan time and imaging dose.

Motion modeling represents the DFM into a linear combination of several weighted spatiotemporal basis functions. Some methods use B-spline based basis functions [39], and other methods use principal component analysis (PCA) based basis
functions [40-44]. Compared with the B-spline based motion modeling, the PCA-based motion modeling is more robust to motion irregularity and is generally faster. In the PCA method, one phase of the prior 4D planning CT is used as the prior image and all other phase images are deformed to the prior image to generate a series of DFM. Then, principal motion modes are extracted using PCA, and the DFM to solve for can be represented by a weighted linear combination of the extracted principal motion modes. The coefficients of the motion modes are optimized by using the data fidelity constraint. The on-board 4D CBCT images are then obtained by deforming the prior CT images using the optimized DFM. Using this PCA model to represent the DFM is valuable in that it reduces the number of variables needed to solve for the DFM. However, the PCA-based motion modeling methods rely on the prior information like 4D planning CT to build a motion model. Substantial breathing pattern and anatomical variations from planning CT to on-board treatment may potentially render the motion model outdated and incorrect, which will affect the on-board image estimation accuracy [47].

To address the limitations in the PCA model, free-form deformation (FD) methods were introduced to estimate CBCT images from prior CT images [45, 48, 49]. Free-form deformation techniques allow the prior CT volume to deform with more flexibility without any assumption of patient motion models. The techniques use deformation energy as a cost function to preserve the smoothness of the deformation field maps. A limitation of using an FD-only method is that there is limited accuracy in
estimating the CBCT using limited angle projections. This is because there is limited
information acquired along the central axis of the limited scanning angles and there are
a large number of variables in the free-form deformation model, which makes the
algorithm more susceptible to getting trapped in a local optimum.

Zhang et al. introduced a motion modeling and free-form deformation (MM-FD)
algorithm, which uses a coarse estimation of the deformation field obtained from the
MM as the input to the FD algorithm. Given the much better starting point from the MM
method, the FD method is able to converge to the optimal DFM$s$ much faster without
getting stuck at local optima. This MMFD method was able to estimate CBCT images
with as few as orthogonal-view 30° scan angles [50, 51] using 102 projections per
respiratory cycle. Figure 1 shows the overall flow chart of the MMFD method [50].
Figure 1: Overall flow chart for the MMFD method [50]. ASD-FD stands for adaptive-steepest-descent free-form deformation.

2.2.2. On-board MRI

MRI integrated with radiotherapy units has been proposed for both inter- and intra-fraction verification [52-56]. Compared to CT, MRI may be more beneficial for certain treating sites since it can provide better soft tissue contrast and has no ionizing radiation dose. Designing a radiotherapy accelerator that also uses an MRI system is difficult because of the magnetic interaction between the two systems; the magnetic field of the MRI alters the accelerator, and the metal of the accelerator alters the homogeneity of the magnetic field inside the MRI. ViewRay (Oakwood Village, Ohio) has developed an MRI-radiotherapy unit that uses a 60Co gamma-ray system, and they have recently developed the MRIdian, an MRI-radiotherapy unit that uses a conventional linear
accelerator (LINAC) system [57, 58]. Elekta and Philips use a high-field (1.5 T) MR-guided linear accelerator (linac) system[56]. Current systems use 2D MR cine images for real-time imaging of moving targets; however they cannot capture the out of plane motion of the target due to the lack of volumetric information.

4D MRI is under development through either prospective or retrospective sorting approaches. For prospective sorting approaches, either fast 2D [52, 59, 60] or 3D MR sequences [54, 61, 62] are used to acquire real-time volumetric images. These approaches suffer from poor temporal and spatial resolution. The retrospective approaches use fast 2D MR sequences to continuously acquire images from all respiratory phases and then retrospectively sort these images by respiratory phase [53, 55, 63-66]. Image acquisition is done in either cine-mode [53, 55, 66] or sequential mode [64, 65]. Liu et al. found that respiratory motion measurements may be more accurate and less susceptible to breathing irregularities in sequential-model 4D MRI than in cine-mode 4D MR [67]. Compared to prospective 4D MRI, motion artifacts are reduced due to more sampling and retrospective sorting, and spatial resolution is improved in retrospective 4D MRI.

2.3. Challenges with Current On-board Imaging Techniques

2.3.1. On-board CBCT

The MM-FD technique developed by Zhang et al. has proven to be effective in generating high quality 4D CBCT images using scanning angles of orthogonal-view 30°.
However, one limitation of this method is that the global PCA model used in the technique assumes a fixed correlation between motion patterns of different anatomical structures in the body from planning-CT to on-board CBCT, which may not be true. The invalidation of this assumption led to estimation errors in the final results when the scan angle was less than orthogonal-view 30°. This prevents us from further reducing the scan angles to reduce the imaging dose and improve the efficiency of the technique for inter- or intra-fraction verification of the target location.

2.3.2. On-board MRI

Currently, the commercial MRI-Radiotherapy systems can generate real-time 2D cine MR images, but not volumetric images for target verification. They cannot capture the out of plane motion of the target due to the lack of volumetric information. 4D-MRI is under development through prospective and retrospective approaches. Limitations to acquiring 4D MRI prospectively are due to current available hardware and software, which make it impossible to acquire high temporal-resolution 4D image sets without significantly compromising image quality. Typical temporal resolution of prospective 4D MRI is greater than 1s, which is insufficient compared to a typical human’s breathing cycle of 4-5 s. The retrospective approach suffers from long acquisition time. Therefore, 4D MRI has limited application for on-board target verification.

No real time volumetric cine MRI has ever been developed due to the limitation of the MR data acquisition speed.
3. Specific Aims

The work presented in this dissertation aims to build upon previous research and develop novel solutions for generating real-time volumetric cine images for both CBCT and MRI by improving both imaging efficiency and accuracy. The completed research dissertation comprises of three major hypotheses and respective aims:

**Hypothesis 1:** The scanning angles of the prior knowledge based CBCT estimation method can be further reduced by improving the patient modeling and free-form optimization.

**Aim 1:** To develop a quasi-real-time cine CBCT reconstruction method using structural PCA and weighted free-form deformation.

**Hypothesis 2:** Real-time 3D MR imaging can be generated using prior knowledge and deformation models.

**Aim 2a:** To develop a volumetric cine (VC)-MRI technique using motion modeling and single slice 2D cine acquisition.

**Aim 2b:** To develop an on-board 4D-MRI technique using limited on-board kV projections from a conventional LINAC and deformation models.
Hypothesis 3: The temporal resolution and geometric accuracy of VC-MRI can be further improved through novel acquisition and reconstruction methods.

Aim 3a: To accelerate VC-MRI through undersampling acquisition while maintaining image quality.

Aim 3b: To improve geometric accuracy of VC-MRI through novel undersampling acquisition and deformation models.

4. Development of a Novel Technique to Generate Quasi-cine CBCT

4.1. Background

Previously, a CBCT estimation method using global motion modeling and free-form deformation (GMM-FD, or previously referred to as ‘MM-FD’ in Section 2.2.1.2.) was developed to estimate 4D CBCT from limited angle projections using prior knowledge and deformation models [50, 51]. As discussed in Section 2.3.1., the global PCA model assumes a fixed correlation between motion patterns of different anatomical structures in the body from planning CT to on-board CBCT, which may not be true. This prevents us from further reducing the scan angles to reduce the imaging dose and improve the efficiency of the technique for inter- or intra-fraction verification of the target location.

In this study, a new structural PCA based motion modeling method was developed to improve the accuracy of the motion modeling by accounting for potential relative motion pattern changes between the target and the body from simulation to
treatment. Weighted free-form deformation was employed to introduce flexibility in adjusting the weighting of different regions in the data fidelity constraint based on the clinical interests. The accuracy of the developed method was evaluated for different patient scenarios and scanning parameters using the XCAT digital phantom and three lung patients’ images, and was compared with the GMM-FD method developed previously.

4.2. Methods and Materials

In the GMM-FD method developed previously [50], each phase of the new on-board CBCT (CBCT\textsubscript{new}) is considered a deformation of the CT volume (CT\textsubscript{prior}) acquired previously for treatment planning. The CBCT\textsubscript{new} at each phase is generated by deforming CT\textsubscript{prior} using a deformation field map (DFM).

\[
CBCT\textsubscript{new}(i, j, k) = CT\textsubscript{prior}(i + D_x(i, j, k), j + D_y(i, j, k), k + D_z(i, j, k))
\]  

\(D_x, D_y, \text{ and } D_z\) represent the deformation fields along the three canonical directions of the Cartesian coordinate system.

To solve for the optimal deformation field, a data fidelity constraint was used, which requires the DRRs of the CBCT\textsubscript{new} to match with the acquired on-board
projections. The GMM-FD method developed previously uses two deformation models to solve the DFM: motion-modeling and free-form deformation. This study had two goals: 1) to develop a motion modeling method that better models the relative motion between the tumor and the body and 2) to add weightings to a region of interest around the tumor within the data fidelity constraint of the free-form optimization to better estimate tumor volume.

4.2.1. Structural-Based PCA Motion Modeling

First, the end expiration phase of an n-phase 4D CT previously acquired for planning is selected as CT\text{prior} in this study due to its relative stability. All of the other (n-1) phases of the 4D CT are deformed to CT\text{prior} using deformable image registration software to obtain (n-1) DFMs. The DFMs are divided into two structures: tumor and body excluding tumor (called ‘body’ from here on out). To determine the region of the tumor structure, the internal target volume (ITV) is estimated from the 4D CT, and then the tumor region used for the structural motion modeling is calculated by taking a rectangular region around the ITV by expanding about 10 mm in the lateral direction, and 15 mm in the AP and SI directions. Then, principal motion modes \{D_{0,tumor}^j\} and \{D_{0,\text{body}}^j\} are extracted from the DFMs for the two structures based on PCA. The deformation field map, D, is represented by a weighted linear combination of the first three principal motion modes for each structure shown in Equation 2.
\[ D = D_{0,ave} + \sum_{j=1}^{3} w_{j,\text{tumor}} \tilde{D}_{0,\text{tumor}}^j + \sum_{j=1}^{3} w_{j,\text{body}} \tilde{D}_{0,\text{body}}^j \]  

\( D_{0,ave} \) is the average of DFMs obtained from the 4D CT, as explained above. The weightings \( w_{j,\text{tumor}} \) and \( w_{j,\text{body}} \) of the PCA eigenvectors are structure specific, and they are the variables to be solved in the algorithm. The data fidelity constraint is used to solve for \( w_{j,\text{tumor}} \) and \( w_{j,\text{body}} \), as shown in Equation 3.

\[ M \ast \text{CBCT}_{\text{new}}(D, \text{CT}_{\text{prior}}) = P \]  

\( M \) represents the projection matrices that project the 3D volume \( \text{CBCT}_{\text{new}} \) to DRRs according to the cone-beam geometry. \( P \) is the onboard projection data acquired. In the clinic, the data fidelity constraint shown in Equation 3 may not be satisfied due to errors caused by the gray level difference between the DRRs and the on-board projections and image artifacts. To solve this problem, the normalized cross correlation (NCC) metric is used for the data fidelity constraint, as was used in a previous study [51]. The data fidelity constraint is then enforced by minimizing the negative value of the NCC as shown in the following objective function:

\[ f(D) = -NCC(M \ast \text{CBCT}_{\text{new}}(D, \text{CT}_{\text{prior}}), P) \]  

A gradient descent optimizer is adopted to minimize the objective function shown in Equation 4. To maintain the smoothness of the deformation field around the boundary between the tumor and body structures, a smoothing constraint is applied after each iteration of the data fidelity optimization. The smoothing constraint is to
minimize the deformation energy around the boundary between the two structures defined in the motion model. The deformation energy of the entire DFM can be defined by Equation 5 [68].

\[
E(D) = \sum_{i=1}^{n_i} \sum_{j=1}^{n_j} \sum_{k=1}^{n_k} \sum_{m=1}^{3} \left( \left( \frac{\partial D_m(i,j,k)}{\partial x} \right)^2 + \left( \frac{\partial D_m(i,j,k)}{\partial y} \right)^2 + \left( \frac{\partial D_m(i,j,k)}{\partial z} \right)^2 \right) 
\]

\[ (5) \]

### 4.2.2. Weighted Free-form Deformation

After the motion modeling optimization, a free-form deformation model is applied to better fine-tune the deformation field voxel by voxel. The free-form deformation model allows each voxel to move independently to meet the data fidelity constraint. Deformation energy (Equation 5) of the entire deformation field is also minimized in the process to regulate the DFMs and preserve their smoothness.

In this study, the FD part of the GMM-FD method was improved by introducing additional weightings in the target region in the data fidelity constraint of the free-form optimization. The weightings were added within a region of interest (ROI) around the tumor in the on-board projections. These weightings give more flexibility in adjusting the importance of matching to different regions in the projection data in the data fidelity constraint based on the clinical interests. The objective function of the data fidelity constraint now becomes the following:

\[
f(D) = -(1 - w)NCC_{global} + wNCC_{ROI} \]

\[ (6) \]
In Equation 6, \( w \) is the weighting coefficient, which ranges from 0 to 1. This allows for flexibility in determining how much importance to put on the whole projection (global) or just to a region around an anatomical structure (ROI). \( w \) equal to 1 represents only matching to the ROI in the projection images, and \( w \) equal to 0 represents matching to the entire global projection image. The ROI is chosen by selecting a region around the planned tumor positions in the projections with a \( \sim 10 \)-15 mm margin added around the tumor. One fixed ROI was selected for a given scan angle since the angular dependence of the ROI location is minimal for the very small scan angles used. For examples, with scan angles of orthogonal-view 15°, one ROI was selected for the projections from 0 – 15°, and a second ROI was selected for projections from 90 – 105°. If the scan angle is single-view 15°, there would be one ROI for the entire 0-15° projections.

The goal of the weighted free-form deformation optimization is now to find the deformation field map \( D \) satisfying Equation 7, subject to the new data fidelity constraint shown in Equation 8

\[
D = \arg\min E(D) \quad (7)
\]

Where \( E(D) \) is the deformation energy.

\[
f(D) = -[(1 - w)NCC_{global} + wNCC_{ROI}] \leq \varepsilon \quad (8)
\]

\( \varepsilon \) here accounts for the fact that DRRs cannot be exactly matched to onboard projections even when the DFMs are perfect. Equation 7 is applied to find the smoothed
DFMs by decreasing the deformation energy while reducing the data fidelity error. To solve the constrained optimization problem, an Adaptive Steepest Descent Free-form Deformation (ASD-FD) algorithm is used similar to the one used in [50]. The deformation energy minimization and the data fidelity constraint are enforced consecutively through gradient descent optimization to adaptively control the step size of the deformation energy minimization to reach final convergence.

The final deformation field is then applied to the CT_{prior} image using Equation 1 to obtain the CBCT_{new} image. Note that the projection data P in the equations are sorted into different phase bins, and the method is applied to projection data from individual phase bins to obtain the CBCT images at each phase.

### 4.2.3. Evaluation Study

Studies using a digital anthropomorphic phantom, XCAT, and three patients’ data [69] were conducted to evaluate the accuracy of the new structural-based motion modeling and weighted free-form deformation method.

#### 4.2.3.1. Simulation Study Using 4D Digital Extended-Cardiac Torso Phantom (XCAT)

A digital anthropomorphic phantom, XCAT, was used to simulate the prior 4D CT set, on-board CBCT images and on-board CBCT projections. XCAT uses nonuniform rational B-spline surfaces to model detailed human anatomy based on databases from the National Library of Medicine and patient datasets [70]. The respiratory motion of both the body volume and user defined lesion volume of the 4D XCAT images can be
controlled separately by two respiratory curves: the diaphragm curve and the chest wall curve. The diaphragm curve mainly determines the motion in the superior-inferior (SI) direction and the chest wall curve mainly controls the motion in the anterior-posterior (AP) direction.

4.2.3.1.1. Prior 4D CT Simulation

A spherical lesion of 30 mm diameter was simulated in the middle of the lung in XCAT. Both the body volume and lesion volume were simulated to move according to the same diaphragm and chest wall curves with a respiratory cycle of 5 seconds. The peak-to-peak amplitudes of the diaphragm curve and the chest wall curve were set to 3 and 2 cm, respectively. This corresponds to lesion peak-to-peak amplitude of 0.8 cm in SI direction and 1.5 cm in AP direction. There was no lateral motion. A ten-phase 4D CT was then simulated as the prior 4D CT. The CT volume of each phase was composed of 256 x 256 x 150 voxels, with each voxel measuring 1.67 x 1.67 x 1.67 mm in dimension. The end-expiration phase of the prior 4D CT was selected as CT_prior.

4.2.3.1.2. On-board Volume and Cone-beam Projection Simulation

On-board patient 4D CBCT sets were generated with the same image size and resolution as 4D CT. To simulate onboard volume sets to reflect different onboard respiratory or anatomical variations, eight patient scenarios were generated.

1. Body volume and lesion move according to the same diaphragm curve and chest wall curve, but peak to peak amplitude of diaphragm curve changes to 2 cm and
that of the chest wall curve changes to 1.2 cm. This corresponds to lesion peak-to-peak amplitude of 0.8 cm in SI direction and 1 cm in AP direction.

2. Based on scenario 1, also with lesion diameter shrinking to 25 mm.

3. Based on scenario 1, also with lesion diameter expanding to 40 mm.

4. Based on scenario 1, also with lesion’s average position shifted in SI direction by 8 mm.

5. Based on scenario 1, also with lesion’s average position shifted in AP direction by 8 mm.

6. Based on scenario 1, also with lesion’s average position shifted in SI, AP and lateral directions by 5 mm each

7. Based on scenario 1, but with lesion having 20% phases shift relative to the body volume respiratory cycle.

8. Body volume and lesion move according to the same diaphragm and chest wall curves as the 4D CT, but the peak-to-peak amplitudes of the diaphragm curve for body and lesion are 2 and 4 cm, respectively; and those of chest wall curve for body and lesion are 1.2 and 3 cm respectively. The lesion peak-to-peak amplitude is 1.2 cm in SI direction and 2.2 cm in AP direction.

Based on the simulated ground-truth 4D CBCT, onboard cone-beam projections of different phases were also simulated based on Siddon’s ray racing techniques [71, 72]. The source to isocenter distance was set to 100 cm, and the isocenter to detector distance
was set to 50 cm. Each projection contains 512 x 384 pixels, with each pixel being 0.78 x 0.78 mm in dimension. Note that the projections were all simulated as full-fan acquisition, which led to a limited field of view (FOV) of ~27 diameter (axial) and ~20 cm length (longitudinal). Part of the phantom was truncated and outside of the FOV.

4.2.3.2. Weighting Coefficient Study

To investigate the effects of weighting coefficients used in the free-form deformation on the estimation accuracy, $w$ values in Equation 8 were set to 0, 0.1, 0.2, 0.5 and 1 for different XCAT scenarios for comparison.

4.2.3.3. Scan Angle and Projection Number Study

To determine the effects of different scan angles on the estimated results of the Structural Motion Modeling and Weighted Free-form Deformation (SMM-WFD) technique in comparison to the previous Global Motion Modeling and Free-form Deformation (GMM-FD) technique, projections of different acquisition scenarios were generated:

1. Single-view 30°
2. Orthogonal-view 15°
3. Orthogonal-view 10°
4. Orthogonal-view 5°

For the single-view 30° acquisition, projections were acquired within one limited scan angle along the AP direction. For the orthogonal-view acquisitions, projections
were acquired within two orthogonal scan angles: AP and left-lateral directions. Two angular spacing techniques were evaluated. The first approach was to set the angular spacing between projections to around 0.5° for all the different acquisition angles. This resulted in acquiring 51, 52, 42, and 22 projections for single-view 30°, orthogonal-view 15°, orthogonal-view 10°, and orthogonal-view 5°, respectively. The second approach was to fix the total number of projections for each acquisition scenario to be 52 projections to investigate the effects of scan angle while fixing the imaging dose. This resulted in setting the angular spacing between projections to 0.6°, 0.4° and 0.2° for orthogonal-view 15°, orthogonal-view 10°, and orthogonal-view 5°, respectively.

To investigate how sparseness of the projection sampling affects the SMM-WFD technique, different numbers of projections were also simulated for orthogonal-view 15° acquisition and orthogonal-view 30° acquisition. For the orthogonal-view 15° acquisition, 52, 22, 12 and 4 projections were simulated and used in evaluation. For the orthogonal-view 30° acquisition, 102, 52, 26, 14, 8 and 4 projections were simulated and used in evaluation.

4.2.3.2. Lesion Contrast Study

To investigate the effects of lesion contrast on the estimation accuracy, various lesion to lung contrast values were investigated. The lung Hounsfield Units (HU) value was set to -700, and lesion HU value was set to -100, -50, 0, 50 and 100 as typical tumor
HU values vary between -100 and 100. This corresponds to a lesion to lung contrast of 600, 650, 700, 750 and 800, respectively.

4.2.3.3. Noise Study

To investigate the effects of noise on the estimation accuracy, we incorporated noise in the projections for the study using patient scenario 2 as an example, similar to the noise study performed in [50]. To summarize, noise was added using MATLAB [The MathWorks, Inc., Natick, Massachusetts] according to Equation 9.

\[
P_i' = -\log_e \left( \frac{\text{Poisson}(I_0 e^{-P_i}) + \text{Normal}(0, \sigma^2)}{I_0} \right)
\]

\[\text{(9)}\]

\(P_i\) is the ray sums of the attenuation coefficients at point \(i\) of each projection. \(I_0\) is set to \(10^5\) to signify intensity of incident photons. Noise was added with the variation level in the normal distribution (\(\sigma^2\)) equal to 0, 10, 50 and 100.

4.2.3.4. Patient Study

Three patients’ data were also used in this study. The images for all three patients were acquired under an IRB-approved protocol at MD Anderson Cancer Center. The 4D CTs were acquired on a CT scanner (LightSpeed, GE Healthcare, Milwaukee, WI) in cine mode. [69] Scan parameters were set at 120 kVp, 100 mA, 0.5 s cine time, and cine duration of average breathing cycle plus 1 s. For 4D CBCT acquisition, 200° on-board full-fan projections of each patient were acquired within two weeks from the 4D CT acquisition, using an adaptive-speed slow-gantry rotation setting [69] using 120 kVp, 80 mA and 25 ms. The projections were phase-sorted using an in-
A house developed Fourier-transform based method. [35, 73] The average sampling intervals of phase-binned projections for patient 1, 2 and 3 are 0.9±1.0°/proj, 0.9±0.9°/proj, and 1.1±1.2°/proj, respectively. Full 200° projections were used to reconstruct the reference clinical 4D CBCT and orthogonal-view 10° projections around the posterior-anterior (PA) (170°~180°) and the right-lateral (RL) (260°~270°) directions were used for the estimation technique. Figure 2 shows an illustration of the scan angles used for the reference and estimated 4D CBCT.

![Figure 2: Illustration of scan angles used for reference 4D CBCT (left) and estimated 4D CBCT (right).](image)

### 4.2.4 Evaluation Methods

The estimation accuracy for lesion location and volume in the on-board CBCT was evaluated at the end-inspiration phase since this phase has the largest deformation from end-expiration CT prior images and therefore the largest estimation errors. This was proven in previous work [50].

For the XCAT study, the lesions were automatically contoured based on a threshold voxel value in both the estimated images and the ground truth CBCT images...
for comparison. Two metrics were defined to quantify the accuracy of the estimated lesion volume: volume percent difference (VPD) and center-of-mass-shift (COMS).

\[
\text{VPD} = \frac{|V \cup V_0 - V \cap V_0|}{V_0} \times 100\% \quad (10)
\]

\(V\) is the lesion volume contoured in the estimated image and \(V_0\) is that contoured in the “ground-truth” image.

\[
\text{COMS} = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2} \quad (11)
\]

\(\Delta x, \Delta y, \Delta z\) are center-of mass distances from \(V\) to \(V_0\).

These accuracy metrics were used to compare between the following methods: 1. Global PCA Motion Modeling (GMM) versus Structural PCA Motion Modeling (SMM) to study the effects of structure based motion modeling; 2. Structural PCA Motion Modeling with Free-form Deformation with no weights (SMM-FD) versus Structural PCA Motion Modeling with Weighted Free-form Deformation (SMM-WFD) to study the effects of weighting in FD; 3. Global PCA Motion Modeling and Free-form Deformation (GMM-FD) versus Structural PCA Motion Modeling with Weighted Free-form Deformation (SMM-WFD) to study the combined effects of structure based motion modeling and weighted FD; 4. Varying the scanning angles and projection numbers.
4.3. Results

4.3.1. XCAT Study

4.3.1.1. Structural PCA

Figure 3 shows the images for prior image, ground-truth (GT) CBCT, estimated CBCT using the global PCA motion model (GMM), and estimated CBCT using the structural based PCA motion model (SMM) based on orthogonal-view 15° scan angle for a) XCAT scenario 5, b) XCAT scenario 6, and c) XCAT scenario 8. Figure 4 shows the subtraction images for GT minus prior, GT minus estimated with GMM and GT minus estimated with SMM for a) XCAT scenario 5, b) XCAT scenario 6, and c) XCAT scenario 8. The images used for ground-truth CBCT and estimated CBCTs were images of the end inspiration phase as to show the most deformation from the prior volume.

Table 1 shows the VPD and the COMS results from CBCTs estimated using GMM and SMM for all eight XCAT scenarios. The results shown in Table 1 are generated from the estimated CBCTs in the end inspiration phase. Using global PCA motion models resulted in a mean VPD and mean COMS of 64.71±30.80% and 5.70±3.92mm across all eight XCAT scenarios using orthogonal-view 15° scan angle, and 63.72±31.30% and 5.96±383 mm using single-view 30°. Using the structural based PCA motion models resulted in a mean VPD and mean COMS of 21.02±9.52% and 0.84±0.55mm using orthogonal-view 15° scan angle, and 31.79±17.62% and 2.69±2.31 mm using single-view 30°.
Figure 3: Comparison of CT\textsubscript{prior} at end-expiration phase, ground-truth CBCT (CBCT\textsubscript{GT}) at end-inspiration phase, estimated CBCT using global MM (CBCT\textsubscript{GMM}) and estimated CBCT using Structural MM (CBCT\textsubscript{SMM}) using orthogonal-view 15° scan
angle with 52 projections for a) XCAT scenario 5, b) XCAT scenario 6, and c) XCAT scenario 8.

Table 1: VPD and COMS for XCAT scenarios with CBCT estimation from global PCA motion modeling (GMM) and Structural based PCA motion modeling (SMM) for single-view 30° projections and orthogonal-view 15° projections. The number of projections was 51 and 52 for single-30° and ortho-15° acquisitions, respectively.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tbody>
<tr>
<td>VPD(%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>53.76</td>
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<td>75.21</td>
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<td>7.87</td>
<td>7.87</td>
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<td>12.70</td>
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<tr>
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<td>1.30</td>
<td>1.99</td>
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<td>0.80</td>
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<td>0.40</td>
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<td></td>
<td></td>
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<tr>
<td>Single 30°</td>
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<td>3.83</td>
<td>4.00</td>
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<td>7.02</td>
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</tr>
<tr>
<td>GMM</td>
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<td>3.40</td>
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<td>3.78</td>
<td>1.75</td>
<td>0.95</td>
<td>7.77</td>
</tr>
<tr>
<td>SMM</td>
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<td>1.30</td>
<td>1.99</td>
<td>0.43</td>
<td>0.70</td>
<td>0.80</td>
<td>0.68</td>
<td>0.40</td>
</tr>
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<td>Ortho 50°</td>
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<tr>
<td>GMM</td>
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<td>2.69</td>
<td>2.87</td>
<td>7.12</td>
<td>7.87</td>
<td>7.87</td>
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<tr>
<td>SMM</td>
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<td>1.30</td>
<td>1.99</td>
<td>0.43</td>
<td>0.70</td>
<td>0.80</td>
<td>0.68</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Figure 4: Subtraction images for axial, coronal and sagittal images shown in Figure 3a, b and c, respectively.

4.3.1.2. Weighted Free-form Deformation

\( w = 0.1 \) was chosen for all the results below labeled ‘SMM-WFD’. Figure 5 shows an example of the ROI chosen within a projection. Figure 6 shows the images for prior image, ground-truth CBCT, estimated CBCT using the global PCA motion model and free form deformation (GMM-FD), and estimated CBCT using the structural based PCA motion model and weighted free form deformation (SMM-WFD) using orthogonal-view \( 15^\circ \) scan angle for a) XCAT scenario 5, b) XCAT scenario 6, and c) XCAT scenario 8. Figure 7 shows the subtraction images for GT minus prior, GT minus estimated with GMM-FD and GT minus estimated with SMM-WFD for a) XCAT scenario 5, b) XCAT scenario 6, and c) XCAT scenario 8. The images used for ground-truth CBCT and estimated CBCTs were images from the end inhalation phase as to show the most deformation from the prior volume.
Figure 5: Example of the ROI selected within a projection image. The weightings would be applied everywhere inside the ROI within the data fidelity constraint of the free-form deformation model.
Figure 6: Comparison of $CT_{\text{prior}}$ at end-expiration phase, ground-truth CBCT ($CBCT_{\text{GT}}$) at end-inspiration phase, estimated CBCT using global MMFD ($CBCT_{\text{GMM-FD}}$) and estimated CBCT using structure MM with weighted FD ($CBCT_{\text{SMM-WFD}}$).
using orthogonal-view 15° projection acquisition with 52 projections for a) XCAT scenario 4, b) XCAT scenario 6 and c) XCAT scenario 8.

Figure 7: Subtraction images for axial, coronal and sagittal images shown in Figure 6a, b and c, respectively.
Table 2 shows the VPD and the COMS results from CBCTs estimated using GMM-FD and SMM-WFD for all eight XCAT scenarios with single-view 30° scan angles, and CBCTs estimated using GMM-FD, SMM-FD, and SMM-WFD for all XCAT scenarios with orthogonal-view 15° scan angles. The results shown in Table 2 are generated from the estimated CBCTs in the end inspiration phase. Using GMM-FD resulted in a mean VPD and mean COMS of 25.23±19.01% and 2.58±2.54mm across all eight XCAT scenarios using orthogonal-view 15° scan angle and 32.00±23.81% and 3.39±3.06mm using single view 30°. Using the SMM-WFD resulted in a mean VPD and mean COMS of 3.47±2.94% and 0.23±0.22mm using orthogonal-view 15° scan angle and 13.82±11.82% and 1.50±1.49mm using single view 30°. Using SMM-FD resulted in a mean VPD and mean COMS of 9.96±4.39% and 0.37±0.20mm using orthogonal-view 15° scan angles.

Table 2: VPD and COMS for XCAT scenarios with CBCT estimation from global PCA motion modeling with free-form deformation (GMM-FD), structural based PCA motion modeling with free-form deformation (SMM-FD) and structural based PCA motion modeling with weighted free-form deformation (SMM-WFD) for different scan angle acquisitions.

<table>
<thead>
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<th>Scenarios</th>
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<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single 30°</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMM-FD</td>
<td>16.11</td>
<td>27.29</td>
<td>30.64</td>
<td>25.97</td>
<td>46.89</td>
<td>19.97</td>
<td>5.99</td>
<td>83.10</td>
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<td>12.17</td>
<td>11.16</td>
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<td>42.26</td>
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<td>Ortho 15°</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>4.57</td>
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<td>2.96</td>
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<td>2.73</td>
<td>5.42</td>
<td>2.05</td>
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</tr>
<tr>
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<td>SMM-WFD</td>
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<td>2.13</td>
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<td>0.66</td>
<td>0.44</td>
</tr>
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<td>Ortho 50°</td>
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<td>0.44</td>
<td>1.03</td>
<td>2.28</td>
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<td>3.95</td>
<td>2.76</td>
<td>0.08</td>
</tr>
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<td></td>
<td>SMM-FD</td>
<td>0.16</td>
<td>0.43</td>
<td>0.46</td>
<td>0.27</td>
<td>0.42</td>
<td>0.73</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>SMM-WFD</td>
<td>0.06</td>
<td>0.15</td>
<td>0.63</td>
<td>0.05</td>
<td>0.18</td>
<td>0.53</td>
<td>0.11</td>
</tr>
</tbody>
</table>

4.3.1.3. Effects of Weighting Coefficient

Table 3 shows VPD/COMS with weighting coefficients $w = 0, 0.1, 0.2, 0.5$ and $1$ for XCAT scenario 2, 5 and 8. $w = 0.1$ was chosen to use in all SMM-WFD results since it provided the best accuracy compared to other weighting coefficient values.

Table 3: Effects of weighting coefficient based on orthogonal-view 15° scan angle with 52 projections using SMM-WFD for XCAT scenarios 2, 5, and 8.

<table>
<thead>
<tr>
<th>$w_{ROI}$</th>
<th>0</th>
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<th>0.5</th>
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<td>VPD(%)</td>
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<td>Scenario 2</td>
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<td>6.24</td>
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<td>2.05</td>
<td>4.18</td>
<td>4.75</td>
</tr>
<tr>
<td>Scenario 8</td>
<td>11.14</td>
<td>2.96</td>
<td>3.50</td>
<td>5.67</td>
<td>6.26</td>
</tr>
<tr>
<td>COMS(mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario 2</td>
<td>0.43</td>
<td>0.15</td>
<td>0.32</td>
<td>0.28</td>
<td>0.25</td>
</tr>
<tr>
<td>Scenario 5</td>
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<td>0.10</td>
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<td>0.14</td>
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<tr>
<td>Scenario 8</td>
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<td>0.16</td>
<td>0.19</td>
<td>0.14</td>
<td>0.25</td>
</tr>
</tbody>
</table>
4.3.1.4. Effects of Scan Angle and Projection Number

Table 4 shows the image estimation results for the SMM-WFD technique using single-view 30°, orthogonal-view 15°, orthogonal-view 10° and orthogonal-view 5° scan angle acquisition for all XCAT scenarios with equal spacing between projections (≈0.5°). It can be observed that 1) orthogonal-view 15° achieved substantially better results than single-view 30° with the same total scanning angle; 2) although the estimation accuracy degrades slightly as the orthogonal-view scan angle decreases, orthogonal-view 10° provides high accuracies in both VPD and COMS. The mean VPD and COMS among all XCAT scenarios for single-view 30° was 13.82±11.82% and 1.50±1.49mm. The mean VPD and mean COMS among all XCAT scenarios for orthogonal-view 15° was 3.47±2.94% and 0.23±0.22mm. Using orthogonal-view 10°, the mean VPD and mean COMS among all XCAT scenarios was 6.21±5.61% and 0.39±0.49mm. Using orthogonal-view 5°, the mean VPD and mean COMS among all XCAT scenarios was 12.64±9.40% and 0.94±1.03mm.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
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<th>3</th>
<th>4</th>
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<tr>
<td>VPD(%)</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Single 30°</td>
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<td>12.17</td>
<td>11.16</td>
<td>5.51</td>
<td>42.26</td>
</tr>
<tr>
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<td>2.12</td>
<td>1.96</td>
<td>4.57</td>
<td>1.65</td>
<td>2.96</td>
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</table>

Table 4: VPD and COMS for XCAT scenarios with CBCT estimation from structural PCA motion modeling with free-form deformation (SMM-WFD) technique using single-view 30° (51 projections), orthogonal-view 15° (52 projections), orthogonal-view 10° (42 projections) and orthogonal-view 5° (22 projections).
Table 5 shows the image estimation results for the SMM-WFD technique using, orthogonal-view 15°, orthogonal-view 10° and orthogonal-view 5° scan angle acquisition for all XCAT scenarios with all using 52 projections. This study shows the effects of scan angle reduction when the imaging dose is fixed.

Table 5: VPD and COMS for XCAT scenarios with CBCT estimation from structural PCA motion modeling with weighted free-form deformation (SMM-WFD) technique using orthogonal-view 15°, orthogonal-view 10°, and orthogonal-view 5°. Each set of scan angle had 52 projections.
Tables 6 and 7 list the image estimation results using different number of projections for orthogonal-view 30° scan angle acquisition and orthogonal-view 15° scan angle acquisition, respectively. XCAT scenario 2 was used in this study as it has both motion pattern change and tumor size change.

Table 6: VPD and COMS for XCAT scenario 2 using orthogonal-view 30° scan angle with varying number of projections.

<table>
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<th>Projection Number</th>
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<tr>
<td>GMM-FD</td>
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<td>7.81</td>
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<td>23.08</td>
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<td>1.14</td>
<td>3.26</td>
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<td>15.59</td>
<td>29.09</td>
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<td>0.92</td>
<td>1.37</td>
<td>1.33</td>
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<tr>
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<td>0.19</td>
<td>0.25</td>
<td>0.47</td>
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Table 7: VPD and COMS for XCAT scenario 2 using orthogonal-view 15° scan angle with varying number of projections.

<table>
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<td>COMS(mm)</td>
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<td>1.03</td>
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<td>0.23</td>
<td>0.55</td>
<td>1.31</td>
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</table>

4.3.1.5. Lesion Contrast Study

Table 8 shows results for tumor estimation accuracy for lesion to lung contrast values of 600, 650, 700, 750 and 800. The lung HU value was set to -700, and lesion HU
value was set to -100, -50, 0, 50 and 100. The SMM-WFD method achieved high accuracy for all tumor HU values typically seen in the clinics. The estimation accuracy was improved as the HU values of the tumor increased with better contrast to the lung.

Table 8: VPD and COMS values for XCAT scenario 2 with various amounts of lesion contrast. Each column corresponds to $HU_{\text{lesion}}$ set to -100, -50, 0, 50 and 100, respectively. Calculations were done using the SMM-WFD technique with 15° orthogonal scan angles (52 projections).

<table>
<thead>
<tr>
<th>$HU_{\text{lesion}}$</th>
<th>-100</th>
<th>-50</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td>6.53</td>
<td>4.35</td>
<td>3.36</td>
<td>2.89</td>
<td>1.75</td>
</tr>
<tr>
<td>COMS (mm)</td>
<td>0.23</td>
<td>0.17</td>
<td>0.23</td>
<td>0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

4.3.1.6. Noise Study

Figure 8 and Table 9 show the results of the noise study. No noise correction like smoothing or filtration has been applied in the image estimation process. The noise level of that within the Poisson distributed noise (shown in Figure 9b) was closer to that seen in a real clinically acquired projection.

Table 9: VPD and COMS for XCAT scenario 2 using orthogonal-view 15° angle (52 projections) and orthogonal-view 30° angle (102 projections) for various levels of noise within the projection data using both the GMM-FD and SMM-WFD methods.

<table>
<thead>
<tr>
<th>VPD(%)</th>
<th>No noise</th>
<th>Poiss Noise</th>
<th>Poiss Noise +Norm(0,10)</th>
<th>Poiss Noise +Norm(0,50)</th>
<th>Poiss Noise +Norm(0,100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortho 30°</td>
<td>GMM-FD</td>
<td>8.14</td>
<td>12.25</td>
<td>14.71</td>
<td>15.52</td>
</tr>
<tr>
<td>SMM-WFD</td>
<td>1.56</td>
<td>6.29</td>
<td>6.39</td>
<td>8.37</td>
<td>11.78</td>
</tr>
<tr>
<td></td>
<td>Ortho 15°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>GMM-FD</td>
<td>13.86</td>
<td>28.48</td>
<td>27.06</td>
<td>31.55</td>
</tr>
<tr>
<td></td>
<td>SMM-WFD</td>
<td>2.89</td>
<td>15.94</td>
<td>15.85</td>
<td>15.33</td>
</tr>
<tr>
<td>COMS(mm)</td>
<td>Ortho 30°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMM-FD</td>
<td>0.53</td>
<td>1.05</td>
<td>1.27</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>SMM-WFD</td>
<td>0.24</td>
<td>0.40</td>
<td>0.48</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Ortho 15°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMM-FD</td>
<td>1.03</td>
<td>2.08</td>
<td>2.00</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>SMM-WFD</td>
<td>0.15</td>
<td>0.43</td>
<td>0.36</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Figure 8: Visual comparison of the same projection and corresponding CBCT images for XCAT scenario 2. The red arrows indicate the level of noise in the bony region of the projection images. The noise level was gradually increased from left to right: (a) No noise, (b) Poisson noise, (c) Poisson noise + normal(0,10), (d) Poisson noise + normal(0,50), and (e) Poisson noise + normal(0,100).

4.3.2. Patient Study

Figure 9 shows the results from the patient study. ‘CTPrior’ image refers to the end expiration phase image of the 4D-CT, ‘Clinical CBCT’ image refers to the CBCT image at end expiration phase reconstructed with 200° projections using FDK, ‘GMM-FD’ image refers to the CBCT image at end expiration phase reconstructed with 10° orthogonal scan angles using the GMM-FD technique, and ‘SMM-WFD’ image refers to CBCT image at end expiration phase reconstructed with 10° orthogonal scan angles using the
SMM-WFD technique. It can be observed that in each case illustrated in Figure 9, the SMM-WFD technique achieved a better match with the clinical CBCT image than the GMM-FD technique when using only 10° orthogonal scan angles.
Figure 9: Patient image results for patient 1 (P1), patient 2 (P2), and patient 3 (P3). ‘CT_{prior}’ image refers to the end expiration phase image of the 4D-CT, ‘Clinical CBCT’ image refers to the CBCT image reconstructed with 200° projections using
FDK in the end expiration phase, ‘GMM-FD’ image refers to the end expiration phase CBCT image reconstructed with 10° orthogonal scan angles using the GMM-FD technique, and ‘SMM-WFD’ image refers to the end expiration phase CBCT image reconstructed with 10° orthogonal scan angles using the SMM-WFD technique. The arrows and horizontal line provide references for evaluating the tumor volume differences in the images.

4.4. Discussions

4.4.1. SMM-WFD vs GMM-FD

The structural-based PCA motion modeling is innovative in that it decouples the correlation between motion patterns of different anatomical structure and allows relative motion between anatomical structures to change from CT to CBCT, which is more clinically realistic. The weighted free form deformation gives extra freedom for adjusting weightings of different regions in the data fidelity constraint to optimize the image estimation accuracy of the region of most clinical interest. The structural based PCA motion modeling along with the weighted free-form deformation methods can improve the accuracy of the 4D CBCT estimation substantially, especially when using extremely small scan angles or low number of projections. This allows us to significantly reduce the imaging dose and time to achieve ultra-fast 4D CBCT imaging for either inter- or intra-fraction verification to improve the treatment accuracy, which is especially critical for SBRT treatments.

Results in Table 1 showed that the CBCT estimation based on structural based PCA motion modeling achieved better accuracy for tumor localization than that of the global PCA motion modeling. Results in Table 2 showed that the CBCT estimation based
on using weightings in the free-form deformation optimization achieved better accuracy than when all structures were weighted equally. This is because more importance was given to the areas within the projection data that included the tumor volume during the optimization.

VPD = 20% and COMS = 2 mm was used as criteria to judge if the estimation accuracy of the method is clinically acceptable. To justify that, different amount of shift of the 3 cm diameter tumor was simulated to simulate different localization errors of the tumor. Calculation showed that a 1 mm, 2 mm and 3 mm center of mass shift of the tumor correspond to VPD = 10.32%, 19.37% and 29.27%, respectively. Considering the voxel size of 1.67 mm³ in the simulation study, and the fact that a 5 mm ITV-PTV margin is typically used in lung SBRT, a clinically acceptable target localization error is <2 mm, which corresponds to VPD ~= 20% and COMS = 2 mm.

4.4.2. Effects of Scanning Angles and Projection Number

Table 2 showed that orthogonal-view 15° scan angle yielded more accurate estimation than single-view 30° scan angle for both GMM-FD and SMM-WFD. Single-view 30° still gave accurate estimation for 7 out of the 8 XCAT scenarios when using the SMM-WFD technique, whereas single-view 30° only gave accurate estimation for 2 out of the 8 XCAT scenarios when using the GMM-FD technique. Table 5 and 6 showed that reducing the scan angles to orthogonal-view 10° and orthogonal-view 5° degraded the estimation accuracy for SMM-WFD as compared to using orthogonal-view 15° scan
angles. However, the SMM-WFD method was still able to achieve less than 20% for VPD and 2mm for COMS for all XCAT scenarios using orthogonal-view 10° scan angles. In contrast, the GMM-FD method failed for most XCAT scenarios even using orthogonal-view 15° scan angles, as shown in Table 2.

Results in Tables 6 and 7 showed that the SMM-WFD method is much more robust than the GMM-FD method against reduction of the projection number. The GMM-FD technique had a significant decrease in accuracy when there were less than 52 projections using orthogonal-view 15° scan angles or less than 26 projections using orthogonal-view 30° scan angles. In contrast, the SMM-WFD technique was robust against reduction of projection numbers down to only 8 projections in total for both orthogonal-view 30° scan angles and orthogonal-view 15° scan angles. Note that this brings projection number down significantly in comparison to [50] which found that 26 projections using orthogonal-view 30° scan angle were needed to maintain the estimation accuracy. It is important to mention that the number of projections here only estimates one phase image of the onboard 4D-CBCT, so for ten phases, the number of projections would need to be multiplied by 10 to estimate the whole 4D-CBCT set. Using 8 projections for one phase image (or 80 projections for entire 4D set) is much smaller than that of a traditional static CBCT scan. This indicates a substantial reduction of the imaging dose to patients.
4.4.3. Effects of Noise

Results in Table 9 showed that the SMM-WFD method was more robust than the GMM-FD method against increasing levels of noise. In both estimation methods, the estimation accuracy declines as the noise level increases. Both the SMM-WFD and GMM-FD methods achieved better accuracy with increased noise when using orthogonal-view 30° scan angles than using orthogonal-view 15° scan angles. Note that the SMM-WFD technique achieved VPD <20% and COMS<2mm even in the highest amounts of noise for the orthogonal-view 15° scan angle.

4.4.4. Convergence Speed Study

Figure 10 shows the convergence plots for estimation of XCAT scenario 8 based on SMM-WFD and GMM-FD using orthogonal-view 15° scan angle with 52 projections. The convergence speed was similar for the two methods. As shown in Figure 9, the data fidelity error of the ROI of the projection images was significantly less for the SMM-WFD technique as compared to the GMM-FD technique.
Figure 10: Data fidelity errors of the GMM-FD and SMM-WFD techniques for image estimation of XCAT scenario 8 using orthogonal-view 15° scan angle with 52 projections. The red-dashed line shows where the motion modeling optimization converges, and where the free-form deformation starts. The data fidelity error was calculated within the ROI around the tumor in the projection data.

4.4.5. Clinical Impact of Reducing Scanning Dose and Scanning Time

Reducing the scanning angle and number of projections needed to accurately reconstruct 4D CBCT can substantially reduce the scanning dose and scanning time for the patient. Santoso et al. found that for a full 4D CBCT acquisition using about 3000 projections resulted in an absorbed dose of ~8.5 cGy [74]. We can assume a linear relationship between projection number and dose. For the patient study in Section 4.3.2., the number of projections for orthogonal-view 10° scanning angle was on average 25
projections/phase (250 projections total) across the three patients. We can estimate the resulting scanning dose would be 0.7 cGy. This is approximately a 12 times decrease in full angle scanning dose.

The scan time for the 200° gantry rotation per patient ranged from 3.3 to 6.6 minutes for the average breath cycle of 3-6 s [22] for the patient study in Section 4.3.2. We can estimate that acquiring orthogonal-view 10° scan angle with 6°/s gantry rotation in between the orthogonal angles would take ~ 10-20 s (for first 10°) + 15 s (for in between orthogonal angles) + 10-20 s (for second 10°). Therefore, the total scanning time for orthogonal-view 10° scanning angles would be 35-55 seconds total compared to 3.3-6.6 minutes using full 200° full fan scanning angles.

4.4.6. Limitations

It is important to note that this study is a first aim at investigating the feasibility of reducing scan angles and number of projections for accurate on-board 4D-CBCT estimation and localization using a structural-based PCA motion model and weighted free form deformation. Two structures were used in the motion model in this study – tumor and body excluding tumor. Results using these two structures yielded accurate estimation for on-board CBCT imaging using as few as orthogonal-view 10° scan angles, or as few as 8 projections using orthogonal-view 15° scan angle, in comparison to orthogonal 30° and 26 projections needed for the previous GMM-FD method. Further investigation will be carried out to build a more comprehensive multiple organ-specific
structures to model the motion pattern of each organ to further improve the estimation accuracy of the method using extremely small scan angles or low number of projections.

Our current studies have been focusing on the application of the developed technique for imaging lung cancer, which typically has high contrast between the tumor and the surrounding lung tissues. It may be more challenging to apply this technique to reconstruct soft tissue structures in a low contrast region, such as the abdominal region. This is a limitation of any deformable registration algorithm for low contrast regions. Contour or control point based deformation models can potentially be used to improve the reconstruction accuracy based on anatomical features in the low contrast region.

Another aspect that was not investigated in this study due to limited patient data is the effects of patient weight loss on the reconstruction accuracy. Patient weight loss would alter the peripheral body volumes, which could affect the reconstruction accuracy of the tumor volume inside the body. In such a scenario, a new planning 4D-CT can be acquired during the treatment course to update the patient anatomy. Also it is worthy to mention that as this technique was developed primarily for SBRT treatment verification, it’s less likely that substantial weight loss will happen due to the short treatment course in SBRT.

Additionally, there may be concerns about the algorithm’s performance when the lesion is located in the upper lobe of lung and the diaphragm is not included in all CBCT projections. We did a XCAT study simulating XCAT scenario 2, but with the
lesion located high in the upper lobes of the lungs. Figure 11 shows the $C_T^{prior}$ and a sample on-board CBCT projection image for the simulation. We found that when using 15° orthogonal scan angles with 52 projections, the GMM-FD method achieved VPD/COMS of 31.10%/1.11mm and the SMM-WFD method achieved VPD/COMS of 13.88%/0.44mm demonstrating the substantial improvements by the SMM-WFD method.

![CT prior and OBI](image)

**Figure 11:** $C_T^{prior}$ and sample on-board CBCT projection image for the XCAT simulation with a tumor in the upper lobe of the left lung.

Lastly, the gray value mismatch between CT and CBCT and image artifacts can potentially affect the accuracy of the reconstruction. Different approaches have been developed in the past to address this issue. Wang et al. [45] and Li et al.[75] proposed to address this issue by linearly scaling the on-board projections, and demonstrated the efficacy of their methods through patient studies. We proposed to address this issue by using normalized cross correlation (NCC) as the data fidelity metric [51], which was proven to be more robust than image differences against intensity mismatches and
artifacts in patient studies. Potential further improvements can be made by incorporating accurate scatter correction algorithms or modeling beam hardening in the projection images [76-80] to improve the performance of current algorithm.

In summary, compared to global PCA MMFD, the structural-based PCA MM with weighted free-form deformation technique can substantially improve the 4D CBCT estimation accuracy using extremely small scan angles and small number of projections to provide ultra-fast low dose 4D target verification in lung radiation therapy.

5. Development of Novel Techniques to Generate Volumetric Cine MRI (VC-MRI)

5.1. VC-MRI Using Prior 4D MRI and On-board 2D Cine MRI

5.1.1. Background

CBCT has been developed for on-board target localization; however, its applications are limited by the long scanning time, high imaging dose and poor soft tissue contrast [81-83]. Previous work, including the work described in 4 has been done to use patient prior knowledge and deformation models for fast estimation of 4D-CBCT with low dose [41-44, 47, 50, 84]. However, MRI is still needed for better soft tissue contrast for imaging tumors in the soft tissue such liver cancer. Currently, commercial MRI-Radiotherapy systems [85] are only capable of generating 2D cine images without volumetric information for real-time verification of moving targets. No real time volumetric cine MRI has been developed due to limitation of the MR data acquisition speed.
In this study, a novel algorithm was developed to generate volumetric cine MRI (VC-MRI) images based on prior images and motion models for real time volumetric target localization in radiotherapy.

5.1.2. Methods and Materials

In VC-MRI, each time step of the VC-MRI images is considered a deformation of the prior MRI images acquired during patient simulation. One phase of the prior 4D MRI was used as the prior image, MRI\textsubscript{prior}. The new on-board VC-MRI at any time-step can be expressed as a function of the Deformation Field Map (DFM), D, and MRI\textsubscript{prior} as shown in Equation 12.

\[
VCMRI(i, j, k) = MRI_{prior}(i + D_x(i, j, k), j + D_y(i, j, k), k + D_z(i, j, k))
\]  

(12)

\(D_x, D_y, D_z\) represent the deformation fields along the three canonical directions of the Cartesian coordinate system. The deformation field D in Eq. (12) has a large number of variables, which makes the searching of the optimal D inefficient and prone to be trapped at locally optimal values. To solve this problem, a PCA-based motion modeling method was used to reduce the number of variables in the deformation field D.

5.1.2.1. PCA Motion Model

Deformation fields were obtained by registering the one phase used as MRI\textsubscript{prior} with all other phases of the prior 4D-MRI images. PCA was used to extract three principal deformation modes \(\{\vec{D}_0\}\) of the patient.
On-board DFM $D$ to be solved in Equation 12 can be expressed as a linear combination of the three principal deformation modes

$$D = D_{\text{ave}} + \sum_{j=1}^{3} w_j D_0^j$$  \hspace{1cm} (13)

$D_{\text{ave}}$ is the average of the original DFM from the prior 4D MRI. $w_j (j=1,2,3)$ are the weightings corresponding to each principal motion mode.

On-board 2D cine MRI images are used for VC-MRI estimation. The weighting coefficients, $w_j (j=1,2,3)$ in Eq. (13), can be solved by using a data fidelity constraint which states that the corresponding 2D slice of the estimated VC-MRI matches with the on-board 2D-cine slice

$$S \ast \text{VCMRI}(D, \text{MRI}_{\text{prior}}) = 2\text{DCine}_{\text{slice}}$$  \hspace{1cm} (14)

Where $S$ is the operator to extract the corresponding 2D slice from the estimated VC-MRI images. This data fidelity constraint is met by minimizing the following objective function:

$$f(w) = \left\| S \ast \text{VCMRI} \left( D_{\text{ave}} + \sum_{j=1}^{3} w_j D_0^j, \text{MRI}_{\text{prior}} \right) - 2\text{DCine}_{\text{slice}} \right\|_2^2$$  \hspace{1cm} (15)

A gradient descent method was used to find the $w_j$ that minimizes $f(w)$.

Once $\tilde{w}$ is solved, the DFM $D$ can be built according to Eq (13). Then, the DFM $D$ can be applied to the prior image to obtain the VC-MRI based on Eq (12).
5.1.2.2. Effect of Acquisition Orientation

Axial, sagittal and coronal 2D cine MR images were all used for VC-MRI estimation separately for both XCAT and patient data. The accuracies of the estimated VC-MRI based on different cine images were compared to investigate the effect of acquisition orientation of 2D cine MR images on the VC-MRI estimation.

5.1.2.3. Effect of Region of Interest (ROI) Selection

In the XCAT study, the VC-MRI was estimated using both the entire image and the ROI surrounding the tumor region in the 2D-cine MR image to evaluate the effect of ROI selection on the estimation accuracy. In the patient studies, the entire 2D cine image was used for image estimation.

5.1.2.3 Simulation using XCAT Phantom

A spherical lesion of 30 mm diameter was simulated in the middle of the lung in XCAT. Both the body volume and lesion volume were simulated to move according to the same diaphragm and chest wall curves with a respiratory cycle of 5 seconds. The peak-to-peak amplitudes of the diaphragm curve and the chest wall curve were set to 3 and 2 cm, respectively. A ten-phase 4D MRI was then simulated as the prior 4D MRI. The MRI volume of each phase was composed of 256 x 256 x 100 voxels, with each voxel measuring 1.875x 1.875 x 3 mm in dimension. The XCAT phantom was generated in the activity mode in order to produce MRI-like images. Signal intensities of organs and
tissues were assigned using values derived from FIESTA/TrueFISP MR images [86]. The end-expiration phase of the prior 4D MRI was selected as MRI$_{\text{prior}}$.

To simulate on-board 2D-cine MR acquisition with a frame rate of 3-5 frames/s as it is typically achievable in a MRI scanner, 21 frames of on-board volumetric MRI images were generated within a respiratory cycle of 5 seconds, with a frame rate of 4 frames/s. These 21 sets of on-board volumetric MRI images were used as the “ground-truth” on-board VC-MRI images. 2D slices were extracted from the ground-truth VC-MRI at the location corresponding to the central slice of the lesion in the MRI$_{\text{prior}}$ images to simulate the on-board 2D-cine MR images acquired.

To evaluate the effects of potential patient breathing pattern change from simulation to treatment, four patient scenarios were simulated for the on-board volumetric cine MRI sets:

1) No breathing pattern change.

2) For both body and lesion volume, the peak-to-peak amplitude of the diaphragm curve changes to 2 cm, and that of the chest wall curve changes to 1.2 cm.

3) Body and lesion move according to the same diaphragm and chest wall curves as prior 4D MRI, but the peak-to-peak amplitudes of the diaphragm curve for body volume and lesion are 4 and 2 cm, respectively; and those of the chest wall curve for body volume and lesion are 3 and 1.2 cm, respectively.
4) Based on scenario 2, but with the lesion having 20% phases shift relative to the body volume respiratory cycle.

5.1.2.3.1. Noise Study

To investigate the effects of noise on the estimation accuracy, noise was incorporated into the 4D-MRI and on-board 2D sagittal cine images for the study using XCAT scenario 2 as an example. The noise was added based on the typical assumption that the MRI signal is governed by a Rayleigh distribution in the presence of noise [87]. To evaluate how the VC-MRI reconstruction method will behave under different magnitudes of noise, SNR levels of 500, 100, 50, and 20 within the lesion were tested.

5.1.2.4. Patient Study Using Liver Cancer Patient Data

The VC-MRI method was evaluated using four liver cancer patients. The patient studies were conducted under an IRB-approved protocol. Details of image acquisition and 4D MRI reconstruction can be found in previous publications [53, 86]. 4D MRI image data were acquired using a fast imaging employing steady state (FIESTA) sequence on a 1.5T GE scanner. The images were retrospectively reconstructed for 10 phases using our in-house developed method, which uses body area of either axial or sagittal MR images as an internal respiratory surrogate for 4D sorting. Each phase consisted of volumetric images of 256 x 256 x 40 voxels, with each voxel measuring 1.875 x 1.875 x 5 mm. The end-inspiration phase was used as MRI\textsubscript{prior}. Single-slice cine MR was acquired separately in axial, coronal and sagittal planes across the center of the tumor.
for 30 s. The image parameters were field of view (FOV): 360 x 240 mm; flip angle: 50°; slice thickness: 5 mm; bandwidth: 976.562 Hz per pixel; acquisition matrix: 192 × 128 for all patients. For two patients (labeled ‘P1’ and ‘P2’ in results section), repetition time (TR)/echo time (TE): 3.005 ms/1.128 ms, corresponding to a frame rate of 2.6 frames/s and for the other two patients (‘P3’ and ‘P4’ in results section), repetition time (TR)/echo time (TE): 2.637 ms/0.948 ms, corresponding to a frame rate of 3 frames/s.

5.1.2.5. Evaluation Methods

The estimation accuracy for lesion location and volume in the on-board VC-MRI was evaluated at every cine time-step, and results were reported as averages across the time-steps with corresponding standard deviations. For the XCAT simulations, the lesions were automatically contoured and the VPD and COMS were calculated based on Equations 10 and 11, respectively.

In addition, the estimation results were evaluated by comparing the image differences and normalized profiles between the estimated and ground-truth VC-MRI.

For the patient studies, a previously developed ROI feature-based motion tracking method [53] was used to calculate and compare the tumor tracking based on VC-MRI and the 2D cine images acquired along different directions. The 2D sagittal cine was used to track the tumor motion along the AP direction, and the 2D coronal cine was used to track the tumor motion along the SI and lateral directions. The tumor tracking curve determined from the sagittal and coronal 2D cine images was used as the
reference to evaluate the accuracy of the tumor tracking curve extracted from the VC-MRI. Since the sagittal and coronal cine images were acquired sequentially instead of simultaneously, there may be some variations of tumor motion from sagittal to coronal cine acquisition. To resolve this issue, the average tumor tracking curves over the 2 minute acquisition for both 2D cine and VC-MRI were used to minimize the effects of breathing variations from cycle to cycle.

5.1.3. Results

5.1.3.1. XCAT Results

Figure 12 shows the prior MRI image (end expiration phase of 4D MRI), ground truth VC-MRI, estimated VC-MRI, as well as their profile comparisons. Figure 13 shows the corresponding subtraction images for XCAT scenario 1. The VC-MRI images were estimated by globally matching with the entire on-board axial 2D cine MRI image. The profile errors between ground-truth VC-MRI and estimated VC-MRI shown in Figure 12 are on average 2.31%, 1.92%, and 3.04% for axial, coronal and sagittal views, respectively. Figure 14 shows the prior image, ground truth VC-MRI and estimated VC-MRI, as well as their profile comparisons. Figure 15 shows the subtraction images for XCAT scenario 2 with simulated noise. The VC-MRI images were estimated by matching with the ROI region of the sagittal 2D cine MRI image with a noise level of SNR = 20. The profile errors between ground-truth VC-MRI and estimated VC-MRI shown in Figure 14 are on average 5.52%, 4.44%, and 3.48% for axial, coronal and sagittal views,
respectively. Note that the ground truth and estimated images of the VC MRIs in both Figures 12-15 were taken from the end-inspiration phase as it has the most deformation from the prior image. Ten iterations were performed before the algorithm reached convergence, which has also been shown in previous PCA studies.[43, 50]

The VPD of the prior image compared with the ground-truth VC-MRI was 66.67±91.95% and COMS was 6.13±8.35 mm on average across all four XCAT scenarios and cine time steps. Table 10a shows the average VPD and COMS across all cine time-steps for different scenarios, acquisition orientations and estimation schemes (matching globally or matching ROI). Table 10b shows the VPD and COMS for the noise study performed on XCAT scenario 2.

Figure 16 shows the centroid locations of the lesion along three axes over four respiratory cycles in the ground-truth images and the estimated VC-MRI for XCAT scenario 2. The VC-MRI estimation scheme used was to match with the ROI around the lesion in the sagittal cine image.
Figure 12: Comparison of prior MRI ($\text{MRI}_{\text{prior}}$) at end-expiration phase, ground-truth on-board VC-MRI ($\text{VCMRI}_{\text{gt}}$) at end-inspiration phase and estimated on-board VC-MRI ($\text{VCMRI}_{\text{est}}$) for XCAT scenario 1. The VC-MRI was estimated using the entire 2D cine-MRI in the axial view. The horizontal red dotted line corresponds to the location of the profile curves shown to the right of the images.
Figure 13: Subtraction images for the axial, coronal and sagittal images shown in Fig. 10
Figure 14: Comparison of $\text{MRI}_{\text{prior}}$ at end-expiration phase, ground-truth VC-MRI ($\text{VCMRI}_{\text{gt}}$) at end-inspiration phase and estimated VC-MRI ($\text{VCMRI}_{\text{est}}$) for XCAT patient scenario 2. VC-MRI was estimated using the ROI around the lesion (the red box) in the 2D cine image in the sagittal view with added noise (SNR = 20). The horizontal red dotted line corresponds to the location of the profile curves shown to the right of the images.
Figure 15: Subtraction images for the axial, coronal and sagittal images shown in Fig. 12. The boxes in images signify the ROI regions used for VC-MRI estimation.
Figure 16: Lesion centroid position curve along different axes for all time steps for XCAT scenario 2. The VC-MRI was estimated using the ROI around the lesion in the sagittal on-board 2D cine image. The solid line corresponds to the ground-truth lesion position, and the dotted line corresponds to the estimated lesion position in VC-MRI.

Table 10: a) VPD and COMS for XCAT scenarios for the six different estimation schemes. b) VPD and COMS for XCAT scenario 2 with various noise levels. The estimation scheme was to match an ROI in the sagittal cine images.

<table>
<thead>
<tr>
<th>XCAT Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial, Global</td>
<td>9.48±2.83</td>
<td>10.74±3.22</td>
<td>52.58±30.89</td>
<td>23.90±11.07</td>
</tr>
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<td>Axial, ROI</td>
<td>11.22±5.07</td>
<td>10.83±4.54</td>
<td>14.09±4.40</td>
<td>10.75±4.25</td>
</tr>
<tr>
<td>Coronal, Global</td>
<td>7.89±1.48</td>
<td>10.65±4.54</td>
<td>56.97±29.56</td>
<td>23.50±12.28</td>
</tr>
</tbody>
</table>
Table 10b.

<table>
<thead>
<tr>
<th></th>
<th>SNR</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500</td>
<td>100</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>VPD(%)</td>
<td>8.22±1.43</td>
<td>8.27±1.47</td>
<td>8.15±1.32</td>
<td>7.95±1.61</td>
</tr>
<tr>
<td>COMS(mm)</td>
<td>0.89±0.54</td>
<td>0.89±0.54</td>
<td>0.99±0.55</td>
<td>0.75±0.55</td>
</tr>
</tbody>
</table>

5.1.3.2 Patient Results

Figure 17 shows the prior MRI image at end-inspiration phase, 2D cine, estimated VC-MRI, as well as their profile comparisons for Patient 1. Figure 18 shows the subtraction images between estimated VC-MRI and 2D cine for Patient 1. Figure 19 shows the tumor tracking based on estimated VC-MRI and 2D cine for average cycles in the lateral, SI and AP directions. Note that the VC-MRI was estimated based on sagittal
cine images, and the tracking along SI and lateral directions were based on the coronal slice of VC-MRI and coronal cine images. The profile errors between 2D cine and estimated VC-MRI shown in Figure 17 are on average 3.87%, 5.88%, and 5.41% for axial, coronal and sagittal views, respectively. Table 11 shows the tracking errors based on VC-MRI for each patient.

**Table 11: Tumor tracking errors (mean, standard deviation and max errors) based on VC-MRI in SI, AP and lateral directions in the patient study. VC-MRI was estimated based on sagittal cine images.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>SI</th>
<th>AP</th>
<th>Lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu \pm \sigma$ (mm)</td>
<td>$\text{error}_{\text{max}}$ (mm)</td>
<td>$\mu \pm \sigma$ (mm)</td>
</tr>
<tr>
<td>Patient 1</td>
<td>0.40±0.40</td>
<td>1.26</td>
<td>0.26±0.30</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.57±0.37</td>
<td>1.35</td>
<td>0.03±0.04</td>
</tr>
<tr>
<td>Patient 3</td>
<td>1.30±0.94</td>
<td>2.64</td>
<td>1.11±0.58</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.55±0.51</td>
<td>1.52</td>
<td>0.87±0.67</td>
</tr>
</tbody>
</table>
Figure 17: a) prior MRI (MRI\textsubscript{prior}), 2D cine MRI and estimated VC-MRI for Patient 1. VC-MRI was estimated by matching to the axial, coronal and sagittal cine images, respectively. The horizontal red dotted line corresponds to the location of the profile curves shown to the right of the images.
Figure 18: Subtraction images for the axial, coronal and sagittal images in Fig 15.
Figure 19: Tracking curves between 2D cine and VCMRI for an average cycle. Note that the VCMRI was generated by matching to sagittal cine images. The tracking along Lat and SI directions were based on the coronal slice of the VCMRI and coronal cine, while tracking along AP direction was based on the sagittal slice of VCMRI and sagittal cine.

5.1.4. Discussions and Summary

VC-MRI is the first technique capable of generating real time volumetric MRI images for target localization in radiation therapy treatments. Different from 2D cine MRI and 4D-MRI, VC-MRI can potentially achieve both high temporal resolution of 3-5 frames/s and high 3D spatial resolution of ~1mm in-plane, 1-3mm plane-to-plane resolution depending on the quality of the prior images. With these significant improvements, VC-MRI allows for the first time to localize the full 3D target volume continuously in real time to improve the localization accuracy of SBRT both before and during the actual treatment. The real time volumetric localization by VC-MRI also make it feasible to perform real time 4D gating or target tracking during treatments, which paves the road to further margin reduction and dose escalation for lung and liver SBRT.
Results in Table 10 showed that the VC-MRI estimation based on the ROI region of the cine MR image achieved better accuracy for tumor localization than that based on the entire cine MR image when there was substantial breathing pattern change from prior to on-board images. This is because the deformation models from prior images were not accurate to model the entire body motion, but were still accurate enough to model the local tumor motion under these scenarios. For the VC-MRI estimation based on the ROI region, sagittal MR cine images produced better estimation accuracy than coronal and axial cine images. This is due to the fact that the sagittal image captured most of the prominent tumor motion along the superior-inferior and anterior-posterior directions, which provided more motion information for the VC-MRI estimation.

Note that the PCA model in this study was built from the deformation fields obtained from the prior 4D-MRI data. In the situation where no 4D-MRI is available, one possible solution is to build the PCA model from deformations obtained from 4D-CT data, as reported in previous studies.[50]

The VC-MRI was evaluated using four liver cancer patients’ data. One limitation in using this data is that it is challenging to establish ground-truth images for patient studies since there is no real-time 3D MRI techniques available. In our study, tumor tracking curves extracted from the 2D cine images were used as references to evaluate the tumor tracking curves determined by the estimated VC-MRI. VC-MRI based on matching to the 2D sagittal cine MRI were used to determine the motion trajectories of
the estimated images. The SI and AP reference tracking curves were based on the 2D coronal cine MRI, and the lateral reference tracking curves were based on the 2D sagittal cine MRI. Because the lateral tracking errors were based on comparing the 2D sagittal cine MRI with the VC-MRI estimated using the 2D sagittal cine MRI, there may be some bias in the results. For the SI and AP directions, however, errors were based on comparing the 2D coronal cine MRI with the VC-MRI estimated using the 2D sagittal cine MRI. In the future, additional evaluation may need to be done to further investigate the VC-MRI estimation using patient studies.

In summary, a novel VC-MRI technique has been developed to use patient prior images, deformation models and real-time on-board 2D cine images to generate volumetric cine MRI images. Preliminary studies using both XCAT simulation of lung cancer patients and real liver cancer patients data demonstrated the feasibility of the VC-MRI technique, which can potentially become a valuable tool for both inter-and intra-fraction target localization in lung and liver SBRT treatments.

5.2. On-board 4D MRI Using Prior 4D MRI and On-board kV Projections from a Conventional LINAC

5.2.1. Background

Compared to CBCT, MRI has no ionizing radiation dose and much better soft tissue contrast, which can significantly improve the localization accuracy of liver SBRT. However, MRI-radiotherapy machines are only available in a very limited number of radiation therapy facilities due to the high cost, which severely limits the usage of MR
for radiotherapy guidance. On the contrary, conventional LINACs with on-board kV imaging systems are widely available in most clinics. Therefore, it is highly desirable to use patient prior MR images and on-board kV imaging systems to generate images with high soft tissue contrasts for target localization.

Previously, deformable image registration (DIR) has been used in the clinic for auto-contouring, treatment planning and dose accumulation in adaptive radiation therapy [88-93]. Recently, a DIR based optimization algorithm was developed to estimate on-board limited angle 4D CBCT and volumetric cine MRI, respectively, using prior images and on-board data acquired within the same modality [50, 84, 94, 95]. At present, no method has been developed to use DIR, prior images and on-board limited kV projections to generate on-board multimodality images to improve the soft tissue localization accuracy.

This study developed a novel approach to generate on-board 4D MRI using a conventional LINAC with an on-board kV imaging system and prior simulation MR images for liver SBRT localization. The method innovatively used patient prior 4D MRI images, on-board limited kV projections, and a deformation field map optimization algorithm to estimate on-board 4D MRI images. The feasibility of the method was evaluated through the digital XCAT phantom and a liver cancer patient.
5.2.2. Methods and Materials

The overall workflow to generate the on-board 4D MRI is shown in Figure 20. Patient 4D MRI is acquired during the simulation stage, and MRI$_{\text{prior}}$ is defined as the end of expiration (EOE) phase of the 4D MRI. The on-board 4D MRI at any respiratory phase is considered a deformation of the MRI$_{\text{prior}}$. The data fidelity constraint is used to solve the DFM based on the limited on-board kV projections acquired. Specifically, MRI$_{\text{prior}}$ is used to generate a synthetic CT at EOE phase (sCT$_{\text{prior}}$). The data fidelity constraint requires the DRRs calculated from the deformed sCT$_{\text{prior}}$ to match with the corresponding on-board kV projections acquired (OBI), as shown in Eq. 16.

$$DRR(DFM, sCT_{\text{prior}}) = OBI$$  \hspace{1cm} \text{Eq. 16}

A previously developed motion modeling and free-form deformation (MMFD) method is used to solve the DFM in the ill conditioned problem defined in Eq. 16.[50, 51] Specifically, MRI$_{\text{prior}}$ is deformably registered to all other phases of the prior 4D MRI to obtain a series of DFMs. PCA is performed on the DFMs to extract the first three principal motion modes. The DFM to be solved is represented by a linear combination of the motion modes with a much fewer number of variables. A free-form deformation model is used afterwards to fine-tune the DFM obtained from motion modeling. Finally, the on-board 4D MRI is generated by deforming the MRI$_{\text{prior}}$ based on the solved DFM.
5.2.2.1. Generating Synthetic CT\textsuperscript{prior} from MRI\textsuperscript{prior}

In order to perform the optimization of the DFMs, a synthetic CT prior, sCT\textsubscript{prior}, is generated so that DRRs can be calculated for matching with the on-board kV projections in the data fidelity constraint defined in Eq. 16. Figure 21 shows a flow chart for generating sCT\textsubscript{prior} from MRI\textsubscript{prior} and a prior 3D CT (i.e., EOE phase from simulation 4D CT). DIR is performed to register the prior 3D CT with the MRI\textsubscript{prior} to generate a deformed CT. Anatomical structures are manually contoured in the MRI\textsubscript{prior} and are
used to correct for any geometrical discrepancies in the deformed CT to generate a corrected deformed CT. In the instance of a mismatch contour between deformed CT and MRI\textsubscript{prior}, the contour from deformed CT is overridden by the one from MRI\textsubscript{prior}. Mean HU values and the noise levels of each structure are derived from the 3D CT volume. Lastly, the mean HU values and noise levels in each anatomical structure in the corrected deformed CT are adjusted to match with those derived from the 3D CT to generate the final sCT\textsubscript{prior}. The sCT\textsubscript{prior} is then used to optimize the deformation field map using the MMFD algorithm.

Figure 21: Workflow used to generate sCT\textsubscript{prior} from a 3D CT and MRI\textsubscript{prior}. 

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5.2.2.2. Initial Estimation of Deformation Field Maps from PCA Based Motion Modeling

$\text{MRI}_{\text{prior}}$ is deformed to all other phase volumes of the 4D MRI to obtain DFMs. The average of the DFMs is calculated and defined as $\text{DFM}_{0,\text{ave}}$. PCA is used to extract patient motion patterns and the motion modeling (MM) optimization is used to get a rough estimation of DFM. The DFM is represented as a weighted linear combination of the motion patterns. The initial starting DFM into the MMFD optimization algorithm is $\text{DFM}_{0,\text{ave}}$, and all weighting coefficients set to zero.

During the MM part of the MMFD algorithm, the weighting coefficients are optimized by using the data fidelity constraint shown in Equation 16, which matches the DRRs from the deformed $\text{sCT}_{\text{prior}}$ to the onboard kV projections. The MM optimization generates a coarse DFM, which is used as the input to the free-form deformation optimization.

5.2.2.3. Fine-tuning the Deformation Field Maps Using Free-form Deformation

In the free-form deformation (FD) optimization, the coarse DFM obtained from the MM is fine-tuned by letting each voxel deform freely to correct any existing errors. In the FD optimization, the data fidelity constraint is met while minimizing the deformation energy of the DFM to preserve the smoothness. After the MMFD optimization, $\text{MRI}_{\text{prior}}$ is deformed based on the final DFM to obtain the on-board MRI at a given respiratory phase.
5.2.2.4. XCAT Simulation

5.2.2.4.1. Prior 4D MRI Simulation

A spherical lesion was generated in the middle of the liver in XCAT. The lesion diameter was 30 mm, the respiratory cycle was 5 seconds, the diaphragm curve amplitude was 3 cm, the chest wall curve amplitude was 2 cm, the image size was 256 x 256 x 150 and the resolution was 1.67x1.67x1.67mm³. The XCAT phantom was generated in activity mode in order to produce MRI-like images. Texture was added using an in-house XCAT-MRI package to produce more realistic MRI images.

5.2.2.4.2. Ground-truth on-board 4D MRI and 4D CT Simulation

Three on-board scenarios were generated to reflect various respiratory changes with similar parameters used to generate the prior 4D MRI, but with the following changes. (1) None. (2) Diaphragm curve and chest wall curve were set to 2 cm and 1.2 cm, respectively, to simulate amplitude decrease in both the SI and AP direction from simulation to treatment. (3) Diaphragm curve and chest wall curve were set to 3 cm and 2.5 cm, respectively, to simulate amplitude increase in the AP direction from simulation to treatment.

For all three scenarios, both 4D MRI and 4D CT XCAT phantoms were generated to represent the ground-truth on-board volumes. To generate the 4D CT, the XCAT was simulated in attenuation-mode using an effective energy used in clinical CT scans. Both
the ground-truth on-board 4D MRI and 4D CT had the same image size and resolution as the prior 4D MRI images.

5.2.2.4.3. On-board kV Projection Simulation

Based on the simulated ground-truth on-board 4D CT, on-board cone beam projections of different phases were simulated as described in Section 4.1.3.1.2.

Projections with the following acquisition schemes were generated. (1) Orthogonal-view 30° scan angle with 102 projections. (2) Orthogonal-view 50° scan angle with 168 projections. (3) Single-view 100° scan angle with 167 projections. (4) Single-view 100° scan angle with 41 projections. (5) Single-view 200° scan angle with 81 projections.

5.2.2.5. Patient Study Using Liver Cancer Patient Data

The on-board 4D MRI method was retrospectively evaluated using one liver cancer patient. The liver cancer patient had both 4D MRI and 4D CT data. The 4D MRI was generated using a balanced steady state free precession (bSSFP) imaging acquisition technique to acquire 2D axial images continuously and then retrospectively sort the images based on respiratory phases [53, 66]. The resolution of the 4D MRI was resized to match the resolution of the 4D CT, which was 1.27 x 1.27 x 2.5 mm³. The 4D MRI data was used as the “prior” 4D MRI and the 4D CT data was used as the “on-board” volumes for the study. Orthogonal-view 30° scan angle CBCT projections (102 total projections) were simulated from the 4D CT data and used as the on-board kV
projections. The same parameters were used to generate the projections as described in 4.1.3.1.2.

5.2.2.6. Evaluation Methods

For the XCAT studies, the estimation accuracy for tumor location and volume in the on-board 4D MRI was evaluated at the end of inspiration (EOI) phase since it has the largest deformation from MRI\textsubscript{prior}. The tumor volumes were automatically contoured in the estimated and ground-truth volumes. Three metrics were defined to quantify the accuracy of the estimated lesion volume: volume percent difference (VPD), volume dice coefficient (VDC), and center-of-mass shift (COMS). Definitions for VPD and COMS can be found in Equation 10 and 11. VDC was defined as shown in Equation 17.

\[ VDC = \frac{2|V \cap V_0|}{|V| + |V_0|} \]  
Eq. 17

Where \(|V|\) and \(|V_0|\) are the numbers of elements in the estimated volume and ground-truth volume, respectively.

For the patient data, a ‘reference’ on-board 4D MRI was generated by deforming the prior 4D MRI to the ‘on-board’ 4D CT phase by phase. The estimated on-board 4D-MRI was then compared with the reference on-board 4D-MRI for evaluation.

5.2.3. Results

5.2.3.1. XCAT Study

Table 12 shows the on-board 4D MRI estimation accuracy for different XCAT scenarios with various scan angles and projections. All values are based on the end of
inspiration (EOI) phase in the on-board images, as it has the largest deformation from the prior data. Figure 22a shows MRI\textsubscript{prior} image, ground-truth on-board CT image in EOI phase, ground-truth on-board MRI image in EOI phase, and estimated on-board MRI image in EOI phase. Figure 22b shows the subtraction images for the axial, coronal and sagittal images shown in Figure 22a.

Table 12: VPD(\%), VDC, and COMS (mm) values for the on-board MRI images for all three XCAT scenarios. All results are shown for the EOI phase images.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho 30°</td>
<td>9.89</td>
<td>9.00</td>
<td>11.58</td>
</tr>
<tr>
<td>Ortho 15°</td>
<td>10.92</td>
<td>8.87</td>
<td>11.80</td>
</tr>
<tr>
<td>Single 100°</td>
<td>9.93</td>
<td>8.61</td>
<td>14.35</td>
</tr>
<tr>
<td>Single 100°</td>
<td>11.87</td>
<td>8.61</td>
<td>13.01</td>
</tr>
<tr>
<td>Single 200°</td>
<td>11.40</td>
<td>7.21</td>
<td>11.15</td>
</tr>
<tr>
<td>VDC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho 30°</td>
<td>0.95</td>
<td>0.96</td>
<td>0.94</td>
</tr>
<tr>
<td>Ortho 15°</td>
<td>0.95</td>
<td>0.96</td>
<td>0.94</td>
</tr>
<tr>
<td>Single 100°</td>
<td>0.95</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>Single 100°</td>
<td>0.94</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>Single 200°</td>
<td>0.94</td>
<td>0.96</td>
<td>0.94</td>
</tr>
<tr>
<td>COMS (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho 30°</td>
<td>0.79</td>
<td>0.80</td>
<td>1.05</td>
</tr>
<tr>
<td>Ortho 15°</td>
<td>0.93</td>
<td>0.76</td>
<td>1.07</td>
</tr>
<tr>
<td>Single 100°</td>
<td>0.82</td>
<td>0.67</td>
<td>1.25</td>
</tr>
<tr>
<td>Single 100°</td>
<td>0.94</td>
<td>0.69</td>
<td>1.04</td>
</tr>
</tbody>
</table>
Figure 22: a) The columns from left to right are the following. MRI\textsubscript{prior} at EOE phase, ground-truth CT at EOI phase, ground-truth on-board MRI at EOI phase and estimated on-board MRI at EOI phase for XCAT Scenario 2. The rows represent axial, coronal and sagittal views, respectively. The horizontal red dotted line and arrows indicate areas for comparison. b) Subtraction images for axial, coronal and sagittal images shown in a).
5.2.3.2. Patient Study

Figure 23 shows prior MRI image at EOE phase, on-board CT at EOI phase, reference on-board MRI at EOI phase and estimated on-board MRI at EOI phase for the patient data. The reference on-board MRI was generated by deforming the EOI phase of the prior 4D MRI to the EOI phase of the on-board 4D CT. The reference on-board MRI visually match well to the estimated on-board MRI.

Figure 23: The columns from left to right show: Prior MRI (MRI_{prior}) at EOE phase, on-board CT at EOI phase, reference on-board MRI at EOI phase and estimated on-board MRI at EOI phase for the patient study. The rows show the axial, coronal and sagittal views, respectively. The horizontal red dotted line and arrows indicate areas for comparison.

5.2.4. Discussion

This is the first technique that uses prior knowledge and on-board limited kV imaging to generate on-board MR images for MR guided radiotherapy (MRgRT). The technique is applicable in all LINACs with kV imaging capabilities, and can significantly enhance the applications of MRgRT in clinics, especially for liver SBRT treatments. The
MR guidance provided by this technique can potentially improve the localization accuracy of liver SBRT, which can lead to better tumor control and lower toxicities paving the road to further margin reduction and dose escalation.

VPD, VDC and COMS were used as metrics for evaluating the accuracy of the on-board 4D MRI. Note that the accuracy that can be achieved is limited by the image resolution of the prior 4D MRI. Since the image resolution was 1.67x1.67x1.67mm³ for XCAT data, COMS within 2 mm was considered acceptable for the on-board 4D MRI estimation. VPD is sensitive to target size, as it is calculated by dividing the target volume differences by the actual target volume size. Assuming the target volume is offset by 2 mm (the tolerance for COMS), the VPD for a 3 cm diameter target is 20%, which was used as the tolerance for VPD in our studies.

Based on the XCAT data, on-board 4D MRI was successfully estimated for all XCAT scenarios using orthogonal-view 30° scan angles with 102 projections, orthogonal-view 50° scan angles with 168 projections, single-view 100° scan angles with 41 projections, single-view 100° scan angles with 167 projection, and single-view 200° scan angles with 81 projections. For the patient data, the estimated on-board 4D MRI images visually matched well with the reference on-board 4D MRI.

This study aimed to investigate the feasibility of generating on-board 4D MRI using prior 4D MRI, limited projections from a conventional LINAC and deformation models. The estimation method utilized a synthetic CT in order to match DRRs to the
on-board projections in the data fidelity constraint. This was just one way to generate DRRs to match to the on-board projections. An alternative method may include generating a DRR from the MRI [96, 97]. Future studies may investigate this method.

It is important to note that this study is the first to aim to investigate the feasibility of using kV projections and prior 4D MRI to generate on-board 4D MRI. This section of the dissertation provides a proof of concept, and future studies are warranted to fully evaluate the innovative technique. Additional patient studies need to be investigated. Currently, we have a limited number of patients that have both 4D MRI and 4D CT images. Also, it is challenging to establish a ground-truth on-board 4D-MRI image for the patient studies, since currently no places can acquire both on-board 4D-CBCT and on-board 4D-MRI in the same treatment room. For this study, a ‘reference’ on-board MRI was used based on deforming the prior 4D MRI to the ‘on-board’ 4D CT, phase by phase, as the standard to compare with the estimated on-board 4D MRI. Future studies may investigate additional ways to effectively evaluate the method. There may also be future studies to further investigate the effect of kV scan angle or number of projections to optimize the scanning time and imaging dose of the on-board kV acquisition for the novel on-board 4D MRI method presented in this work. Lastly, the current study used a single prior MRI set for generation of on-board 4D-MRI. In the future, multiple prior MRI sets with different contrasts may be used to generate on-
board multi-contrast 4D-MRI from on-board kV imaging acquisition to further improve the localization accuracy.

6. Enhanced Speed and Accuracy of VC-MRI through Novel Acquisition and Estimation Schemes

6.1. Accelerating VC-MRI using a single 2D undersampled cine image

6.1.1. Background

A volumetric cine MRI (VC-MRI) technique has been developed previously to use prior patient images, deformation models and real-time on-board 2D cine images to generate real-time 3D MRI images for both inter- and intra-fractional target localization [94, 98, 99]. Details regarding this method can be found in Section 5.1. The previous technique [94] uses a single, fully sampled 2D cine image to generate VC-MRI at a temporal resolution of 3-5 frames/s, which may not be sufficient to track a moving target for patients with short or irregular breathing cycles [100, 101]. Higher temporal resolution is also needed for VC-MRI to achieve better accuracy for post treatment accumulated dose evaluation and for deriving the tumor motion probability density function (PDF) for probability based treatments [11]. Using accelerated 2D cine images also makes it feasible to acquire multiple 2D cine images at different locations for VC-MRI estimation to potentially improve its accuracy while maintaining a high temporal resolution. In this study, we investigate the feasibility of accelerating the temporal resolution of the VC-MRI by using undersampled 2D cine MRI to provide real-time 3D
images of the patient. Two undersampling acquisition strategies were investigated, including Cartesian k-space undersampling and radial k-space undersampling. The effects of k-space sampling percentage and distribution, tumor sizes and noise on the VC-MRI estimation were investigated using both digital phantom and real patient data.

6.1.2. Methods and Materials

6.1.2.1. VC-MRI Estimation Method

4D MRI are acquired during the patient simulation stage. Patient respiratory motion modes are extracted from the deformation fields generated from the 4D-MRI data using principal component analysis (PCA). One phase of the prior 4D MRI is selected as the prior images designated as MRI\textsubscript{prior}. The on-board VC-MRI images at each time step is considered as a deformation of MRI\textsubscript{prior}. The deformation field for VC-MRI is represented as a linear combination of the prior motion modes, and the weightings for the motion modes are solved by matching to the on-board 2D cine MR images acquired in the data fidelity constraint. VC-MRI is then generated by deforming the MRI\textsubscript{prior} based on the deformation field solved.

A more detailed explanation of how the VC-MRI was estimated can be found in Section 5.1.2.

6.1.2.2. On-board Cine MRI Undersampling Acquisition

The on-board 2D cine MR images were retrospectively undersampled in k-space in order to substantially accelerate the VC-MRI to an ultrafast frame rate. Different
undersampling acquisitions, including Cartesian-based sampling and radial-based sampling were studied to investigate the effect of sampling on the accuracy of the estimated VC-MRI. For each undersampling acquisition, sampling percentage (SP) was defined as the percentage of the full k-space sampling. For an image size of 256 x 256, full k-space sampling has 256 phase encoded lines sampled for Cartesian-based sampling and 402 (256*π/2) spokes sampled for radial-based sampling. The undersampled k-space data were used to reconstruct the 2D cine image using an iterative MR reconstruction algorithm with total generalized variation (TGV) regularization [102]. The TGV reconstruction algorithm uses an inverse problem with a penalty term of TGV theory. The main optimization equation used to reconstruct the k-space data is shown in Equation 18.

\[
\arg\min_u \|F(u) - k\|^2_2 + \beta \text{TGV}^2(u) \quad (18)
\]

Where \( u \) represents the reconstructed image, \( F \) represents the Fourier transform, \( k \) represents the undersampled k-data data, and \( \beta \) represents the regularization parameter for the TGV penalty term. The TGV penalty term allows for regularizing the features on both the smooth and sharp regions of the image. More details regarding the TGV regularization reconstruction method can be found in the reference [102]

VC-MRI was then estimated using the 2D cine MRI reconstructed from the undersampled data. VC-MRI estimated from the fully sampled 2D cine MRI was also generated for comparison.
6.1.2.2.1. Cartesian-Based Variable Density Sampling

Sampling profiles defined in a Cartesian coordinate system are straightforward and are suitable for easy implementation. In this study, variable density sampling along the phase-encoding direction was employed. For a Cartesian based undersampling with certain SP, k-space was sampled continuously from the center for a certain amount, and the rest of the k-space was sampled randomly. The central percentage (CP) was defined as the percentage of SP sampled continuously from the center. Various Cartesian-based undersampling strategies were employed to investigate the effect of SP and CP on the VC-MRI estimation scheme. SP of 50%, 30%, 20% and 10% were investigated to evaluate the effect of total k-space sampled. Due to the fact that SP = 50% and 30% provided no additional useful information in the VC-MRI estimation accuracy, this dissertation only consists of results using SP of 20% and 10%, corresponding to an accelerated frame rate (FR) of 5x and 10x, respectively. For each SP (SP = 20% and SP = 10%), CP of 90%, 70% and 50% were investigated.

6.1.2.2.2. Radial-Based Sampling

In radially sampled MRI, the k-space was sampled with equally spaced radial lines, all of which traversed the center of k-space. Undersampling in the azimuthal direction maintains the overall image structure and results in streaks instead of backfolding or discrete ghosting artifacts typically observed with Cartesian sampling. In this work, undersampled radial-based k-space data were generated by retrospectively
undersampling full k-space data defined on a Cartesian grid along radial sampling lines [103]. Two radial sampling schemes were explored. The first sampling scheme used spokes spaced by the golden angle, i.e. constant azimuthal increment of 111.25°, with spoke numbers $N = 32$ and 21 used to sample the 2D cine MRI k-space data. The spoke numbers were chosen based on previous publications [102]. This golden angle of 111.25° is related to the Golden Ratio and causes radial lines to be evenly spaced with time [104]. The second radial sampling scheme used was based on even-distributed sampling profiles, with azimuthal increments of 5.625° and 8.57° which result in spoke numbers $N = 32$ and 21, respectively. The radial sampling with 32 and 21 spoke numbers represents a k-space SP of approximately 8% and 5.2%, respectively.

6.1.2.3. Simulation Study Using XCAT Phantom

A digital anthropomorphic phantom, 4D Extended Cardiac-Torso (XCAT) [70], was used to simulate the prior 4D MRI set, the onboard ground-truth VC-MRIs and the 2D cine MRIs. Prior 4D MRI and ground-truth VC-MRI with four on-board scenarios were generated as described in Section 5.1.2.3.

Two-dimensional slices were extracted from the ground-truth VC-MRI at the location corresponding to the central slice of the tumor in the MRI

$_{\text{prior}}$ image to simulate fully-sampled on-board 2D cine MRI acquired. The resolution of the 2D cine images was $1.875 \times 1.875 \text{ mm}^2$ and the slice thickness was 3.000 mm. These fully-sampled on-board 2D cine MR images were then transformed to k-space using direct Fourier
transformation, and undersampled for the different undersampling acquisition strategies described above.

Based on results presented in Section 5.1.3., using fully sampled cine images showed that matching to a region-of-interest (ROI) around the tumor in the sagittal cine image resulted in the best VC-MRI accuracy across all XCAT scenarios. Because of this, VC-MRI generated in this study were based on matching to an ROI in the sagittal undersampled cine images.

6.1.2.3.1. Noise Study

To investigate the effects of noise on the estimation accuracy of the accelerated VC-MRI, noise was incorporated into the 4D MRI and the undersampled 2D sagittal cine images for XCAT scenario 2, using a previously reported method [94]. The noise was added based on the assumption that the MRI signal is governed by a Rayleigh distribution in the presence of noise [105]. Signal-to-noise ratio (SNR) levels of 500, 100, 50 and 20 within the tumor based on the cine images in image space were tested.

6.1.2.3.2. Tumor Size Study

To evaluate the effect that tumor size has on the estimation accuracy, a 4D MRI image set was generated with similar properties as described above, with the tumor diameter instead being 40 mm and 20 mm. The on-board VC-MRI images were generated based on a breathing pattern change of scenario 2 for the various tumor sizes.
Cartesian-based undersampling with \( \text{SP} = 20\% \), \( \text{CP} = 90\% \) and \( \text{SP} = 10\% \), \( \text{CP} = 90\% \) were used for 2D cine image acquisition.

6.1.2.4. Patient Study

The accelerated VC-MRI technique was evaluated using 4 liver cancer patients, scanned on a GE Scanner under an institutional review board-approved protocol. Details of image acquisition and 4D MRI reconstruction can be found in Section 5.1.2.4. [53, 66, 86, 94]. For this study, both Cartesian and radial undersampling acquisition were investigated by retrospectively undersampling the 2D cine images acquired in the k-space. \( \text{SP} = 20\% \) with \( \text{CP} = 90\% \) was used for the Cartesian sampling, and \( N = 32 \) spokes spaced by the golden angle was used for the radial sampling. The undersampled 2D cine images were then reconstructed from the undersampled k-space data using the TGV iterative method. It is important to note that both the Cartesian and radial undersampled k-space data was retrospectively sampled from the original fully-sampled Cartesian-based k-space data.

6.1.2.5. Evaluation Methods

For the XCAT studies, the estimation accuracy for tumor location and volume in the on-board VC-MRI was evaluated at every cine time-step, and the results were reported as averages across the time-steps with corresponding standard deviations. Tumors were automatically contoured in 3D in an in-house MATLAB (MathWorks, Natick, MA) code based on a threshold voxel value in both the estimated images and the
ground-truth VC-MRI images for comparison. Two metrics were defined to quantify the accuracy of the estimated tumor volume: volume percent difference (VPD) (Equation 10) and center-of-mass shift (COMS) (Equation 11).

For the patient studies, a previously developed ROI feature-based motion tracking method [53] was used to calculate and compare the tumor tracking based on VC-MRI and the 2D cine images acquired along different directions. Details about the tracking method can be found in Section 5.1.2.5. Pearson correlation coefficients were also calculated between the tumor tracking curves extracted from the 2D cine images and the estimated VC-MRI.

### 6.1.3. Results

VC-MRI generated using fully-sampled cine images were used as the reference for comparison with the VC-MRI generated using undersampled cine images, and will be referred to as ‘reference’ for the remainder of this section.

#### 6.1.3.1. XCAT Study

##### 6.1.3.1.1 Cartesian-based Variable Density Sampling

Table 13 shows the VC-MRI estimation accuracy for different scenarios using 2D cine MR sampled with SP = 20% and 10% and various CP in the k-space. The first column describes the amount of SP and CP that the VPD and COMS numbers correspond to. The second, third, fourth and fifth columns show the results for the XCAT scenarios 1, 2, 3 and 4, respectively. The top half of the table shows the VPD
values and the bottom half of the table shows the corresponding COMS values. Figure 24a shows prior MRI image (end expiration phase of prior 4D MRI), ground-truth VC-MRI, estimated VC-MRI and their profile comparisons to provide qualitative comparisons of the estimated images. The cine MR used for VC-MRI estimation was sampled with SP = 10% and CP = 90%. Based on the profile curves and figures, the estimated VC-MRI matched well to the ground-truth VC-MRI. Figure 24b shows the subtraction images for the axial, coronal and sagittal images shown in Figure 24a, as well as the subtraction images between ground-truth VC-MRI and estimated VC-MRI using fully sampled cine image for comparison. From the subtraction images, the estimated VC-MRI using fully sampled cine images and the estimated VC-MRI using undersampled cine images both showed minimal difference from the ground-truth VC-MRI in the target region.

Table 13: Comparison for SP = 20% and SP = 10% with various amounts of CP. VPD and COMS results were averaged across all cine time-steps. The reference row corresponds to VC-MRI generated with cine images using SP = 100%.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VPD(%)</td>
<td>VPD(%)</td>
<td>VPD(%)</td>
<td>VPD(%)</td>
</tr>
<tr>
<td>Reference (SP = 100%)</td>
<td>9.52±1.74</td>
<td>8.96±1.43</td>
<td>8.98±1.51</td>
<td>8.93±1.47</td>
</tr>
<tr>
<td>CP (SP = 20%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>10.78±2.83</td>
<td>9.01±2.04</td>
<td>11.54±3.37</td>
<td>11.54±3.37</td>
</tr>
<tr>
<td>Percentage</td>
<td>Value 1 ± Standard Deviation</td>
<td>Value 2 ± Standard Deviation</td>
<td>Value 3 ± Standard Deviation</td>
<td>Value 4 ± Standard Deviation</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>70%</td>
<td>10.10±1.84 ± 9.31±1.77</td>
<td>10.95±4.17</td>
<td>11.81±4.57</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>10.52±2.10 ± 9.79±2.24</td>
<td>11.60±3.58</td>
<td>12.41±4.56</td>
<td></td>
</tr>
<tr>
<td>CP (SP = 20%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>10.89±2.87 ± 10.17±3.70</td>
<td>12.73±5.73</td>
<td>13.91±5.94</td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>13.51±5.25 ± 11.96±4.85</td>
<td>14.45±6.64</td>
<td>14.25±6.36</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>18.48±8.52 ± 16.01±6.72</td>
<td>20.63±9.11</td>
<td>18.61±8.73</td>
<td></td>
</tr>
</tbody>
</table>

**COMS (mm)**

<table>
<thead>
<tr>
<th>Reference (SP = 100%)</th>
<th>0.53±0.20</th>
<th>0.43±0.20</th>
<th>0.43±0.21</th>
<th>0.43±0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP (SP = 20%)</td>
<td>0.73±025</td>
<td>0.61±0.31</td>
<td>0.79±0.47</td>
<td>0.79±0.47</td>
</tr>
<tr>
<td>90%</td>
<td>0.63±0.23</td>
<td>0.53±0.24</td>
<td>0.75±0.55</td>
<td>0.92±0.61</td>
</tr>
<tr>
<td>70%</td>
<td>0.71±0.30</td>
<td>0.61±0.32</td>
<td>0.86±0.53</td>
<td>0.98±0.62</td>
</tr>
</tbody>
</table>

**CP (SP = 10%)**

| 90% | 0.80±0.31 | 0.72±0.36 | 1.00±0.61 | 1.07±0.78 |
| 70% | 1.12±0.71 | 1.03±0.63 | 1.33±0.83 | 1.29±0.78 |
| 50% | 1.78±1.05 | 1.53±0.82 | 2.08±1.11 | 1.81±1.06 |
Figure 24: a) Comparison of prior MRI (MRI\textsubscript{prior}) at end-expiration phase, ground-truth on-board volumetric cine-MRI (VCMRI\textsubscript{GT}) at end-inspiration phase and estimated on-board VCMRI (VCMRI\textsubscript{Acc,Est}) for XCAT Scenario 2. ‘Acc’ refers to VCMRI based on accelerated 2D cine images. The undersampled sagittal cine image was acquired using SP = 10\% and CP = 90\%. The horizontal red dotted line corresponds to
the location of the profile curves shown to the right of the images. b) Subtraction images for axial, coronal and sagittal images shown in a). The subtraction images between ground-truth VC-MRI and estimated VC-MRI based on fully sampled cine images are also shown for comparison.

6.1.3.1.2 Radial-Based Sampling

Data in Table 14 shows VPD and COMS values for estimation based on various amounts of radial sampling in the sagittal cine images across all XCAT scenarios. Using the golden angle distribution resulted in slightly better accuracy than using even distribution.

Table 14: Comparison among various amounts of radial sampling using the golden angle and even distribution VPD and COMS results were averaged across all cine time-steps. The reference row corresponds to VC-MRI generated with cine images using SP = 100%.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference (SP = 100%)</td>
<td>9.52±1.74</td>
<td>8.96±1.43</td>
<td>8.98±1.51</td>
<td>8.93±1.47</td>
</tr>
<tr>
<td>Spoke Number</td>
<td>SP(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8</td>
<td>Golden Angle</td>
<td>9.92±1.72</td>
<td>9.54±1.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Even Distribution</td>
<td>10.16±1.81</td>
<td>9.71±1.94</td>
</tr>
<tr>
<td>21</td>
<td>5.2</td>
<td>Golden Angle</td>
<td>10.75±2.03</td>
<td>10.26±1.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Even Distribution</td>
<td>11.24±1.71</td>
<td>12.47±3.78</td>
</tr>
<tr>
<td>COMS(mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference (SP = 100%)</td>
<td>0.53±0.20</td>
<td>0.43±0.20</td>
<td>0.43±0.21</td>
<td>0.43±0.20</td>
</tr>
<tr>
<td>Spoke Number</td>
<td>SP(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8</td>
<td>Golden Angle</td>
<td>0.59±0.21</td>
<td>0.55±0.23</td>
</tr>
</tbody>
</table>
6.1.3.1.3. Effects of Noise

Table 15 shows VPD and COMS values for XCAT scenario 2 with various amounts of noise added to the undersampled sagittal cine images. The Cartesian-based sampled images were generated by sampling 10% of total k-space (SP = 10%) with 90% of that sampled in the center k-space (CP=90%). The radial-based sampled images were generated by sampling with the golden angle using 21 spokes. VC-MRI was robust against increasing noise levels for both Cartesian-based and radial-based undersampling.

Table 15: VPD and COMS for XCAT scenario 2 with various amounts of noise added to the undersampled cine images. VPD and COMS results were averaged across all cine time-steps. The reference row corresponds to VC-MRI generated with cine images using SP = 100%.

<table>
<thead>
<tr>
<th>SNR</th>
<th>500</th>
<th>100</th>
<th>50</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>SP = 100%</td>
<td>9.52±1.74</td>
<td>8.96±1.43</td>
<td>8.98±1.51</td>
</tr>
<tr>
<td>SP(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartesian</td>
<td>10</td>
<td>10.28±2.44</td>
<td>9.84±2.75</td>
<td>10.54±2.87</td>
</tr>
<tr>
<td>Radial, GA</td>
<td>5.2</td>
<td>11.00±2.68</td>
<td>10.10±2.19</td>
<td>10.54±2.92</td>
</tr>
</tbody>
</table>
### 6.1.3.1.4 Effects of Tumor Size Change

Data in Table 16 shows VPD and COMS values for XCAT Scenario 2 using a 20 mm, 30 mm and 40 mm diameter tumor. Cartesian-based undersampling was used in this study. Results shown are for the end-inspiration time-step. The term ‘reference’ refers to VC-MRI estimation based on using a fully sampled sagittal cine image. With a decreased tumor size of 20 mm, the VC-MRI accuracy decreased when undersampling percentage decreased. With an increased tumor size of 40 mm, the VC-MRI was accurate with both SP = 20% and SP = 10%.

Table 16: VPD and COMS values for XCAT Scenario 2 using a 20 mm, 30 mm and 40 mm diameter tumor. Cartesian-based undersampling was used. Both the 20% and 10% k-space images were sampled with CP = 90%. Results shown correspond to the end-inspiration phase of the VC-MRI. Here, ‘reference’ refers to VC-MRI estimation based on using a fully sampled sagittal cine image (SP=100%).

<table>
<thead>
<tr>
<th>Reference</th>
<th>SP = 100%</th>
<th>SP = 20%</th>
<th>SP = 10%</th>
<th>SP = 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartesian</td>
<td>10</td>
<td>0.65±0.30</td>
<td>0.63±0.40</td>
<td>0.75±0.38</td>
</tr>
<tr>
<td>Radial</td>
<td>5.2</td>
<td>0.71±0.39</td>
<td>0.62±0.25</td>
<td>0.67±0.31</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Reference</th>
<th>SP = 20%</th>
<th>SP = 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(SP = 100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VPD(%)</th>
<th></th>
</tr>
</thead>
</table>

99
<table>
<thead>
<tr>
<th>Tumor Diameter</th>
<th>20 mm</th>
<th>30 mm</th>
<th>40 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMS(mm)</td>
<td>0.68</td>
<td>0.29</td>
<td>0.72</td>
</tr>
</tbody>
</table>

6.1.3.2. Patient Study

In the patient studies, the 2D cine images acquired were considered as the corresponding slices of the ground-truth VC-MRI to evaluate the accuracy of the estimated VC-MRI based on undersampled cine images. Figure 25 shows prior MRI image at end-inspiration phase, 2D cine at an end-expiration phase, estimated VC-MRI at an end-expiration phase and their normalized profile comparisons for patient 1. Figure 26 shows subtraction images between estimated accelerated VC-MRI and 2D cine for patient 1, as well as the subtraction images for 2D cine and estimated VC-MRI based on fully sampled cine images. Note that the accelerated VC-MRI was estimated based on SP = 20%, CP = 90% on Cartesian grid in the axial, sagittal and coronal cine images. The red arrows indicate the areas for comparison. Figure 27 shows the tumor tracking based on the fully sampled 2D cine images at different views, the estimated VC-MRI based on
the fully sampled 2D cine images and the estimated VC-MRI based on the undersampled 2D cine images for average cycles in the lateral, SI and AP directions [94].

The accelerated VC-MRI and non-accelerated VC-MRI were estimated based on sagittal cine images. The tracking along the SI and lateral directions were based on the coronal slice of the accelerated VC-MRI and non-accelerated VC-MRI and coronal 2D cine images, and the tracking along the AP direction was based on sagittal slices. Table 17 shows the mean and standard deviation, as well as the Pearson correlation coefficient, of the target tracking accuracy based on VC-MRI using fully sampled 2D sagittal cine images and accelerated VC-MRI using undersampled 2D sagittal cine images for various undersampling acquisition strategies in each patient. All Pearson correlation coefficients were greater than 0.900.

Figure 25: Prior MRI image at end-inspiration phase, 2D cine at an end-expiration phase, estimated VC-MRI for patient 1. VC-MRI was estimated by matching to undersampled axial, coronal and sagittal cine images, respectively. The
undersampled cine images were generated by using $\text{SP} = 20\%$ and $\text{CP} = 95\%$.
Horizontal red dotted lines correspond to the location of the normalized profile curves, shown to the right of the images. The red arrows indicate the areas for comparison.

Figure 26: Subtraction images for axial, coronal and sagittal images shown in a). The subtraction images between 2D cine and estimated VC-MRI based on fully sampled cine images are also shown for comparison. The red arrows indicate the areas for comparison.
Figure 27: Tumor tracking curves based on 2D cine, VC-MRI using full sampled sagittal cine images (VC-MRI_{est}), and VC-MRI using Cartesian-based undersampled sagittal cine images (VC-MRI_{acc,est}) for an average cycle (SP=20%, CP=90%). The tracking along the lateral and superior-inferior directions was based on the coronal slice of the accelerated VC-MRI and non-accelerated VC-MRI and coronal cine, whereas tracking along the anterior-posterior direction was based on the sagittal slice of accelerated VC-MRI and non-accelerated VC-MRI and sagittal cine.

Table 17: Tumor tracking errors (\(\mu\pm\sigma\) (mm)) and Pearson correlation coefficients (PCC) based on comparing estimated VC-MRI with 2D sagittal and 2D coronal cine images in SI, AP and lateral directions for the patient study. Reference VC-MRI is based on using fully sampling cine images (SP=100%). Cartesian-based undersampling VC-MRI_{acc} were generated with SP = 20% and CP = 90%. Radial-based undersampling VC-MRI_{acc} were generated with using the golden angle and N = 32 spokes (SP = 8%).

<table>
<thead>
<tr>
<th>Patient</th>
<th>SI</th>
<th></th>
<th></th>
<th>AP</th>
<th></th>
<th></th>
<th>LAT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\mu\pm\sigma) (mm)</td>
<td>PCC</td>
<td>(\mu\pm\sigma) (mm)</td>
<td>PCC</td>
<td>(\mu\pm\sigma) (mm)</td>
<td>PCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Reference VC-MRI</td>
<td>0.52±0.46</td>
<td>0.982</td>
<td>0.21±0.09</td>
<td>0.998</td>
<td>0.28±0.14</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cartesian-based VC-MRI_{acc}</td>
<td>0.40±0.37</td>
<td>0.987</td>
<td>0.30±0.28</td>
<td>0.978</td>
<td>0.07±0.05</td>
<td>0.997</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radial-based VC-MRI_{acc}</td>
<td>0.46±0.27</td>
<td>0.995</td>
<td>0.21±0.20</td>
<td>0.989</td>
<td>0.14±0.07</td>
<td>0.993</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Reference VC-MRI</td>
<td>0.32±0.17</td>
<td>0.985</td>
<td>0.04±0.02</td>
<td>0.999</td>
<td>0.56±0.54</td>
<td>0.929</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cartesian-based VC-MRI_{acc}</td>
<td>0.56±0.36</td>
<td>0.956</td>
<td>0.38±0.20</td>
<td>0.968</td>
<td>0.57±0.56</td>
<td>0.927</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radial-based VC-MRI_{acc}</td>
<td>0.51±0.43</td>
<td>0.939</td>
<td>0.11±0.03</td>
<td>0.997</td>
<td>0.61±0.33</td>
<td>0.941</td>
<td></td>
</tr>
</tbody>
</table>
### 6.1.4. Discussion

Patient data showed that we can achieve high quality and high temporal resolution VC-MRI using ultra-fast cine images acquired with 10-20% SP for various undersampled acquisition strategies, which corresponds to a 5-10 times acceleration rate of the temporal resolution. This improvement of temporal resolution can potentially improve the localization/tracking accuracy based on VC-MRI to minimize the treatment errors of SBRT to improve the tumor control and minimize the normal tissue toxicities.

VPD and COMS were used as metrics for evaluating the accuracy of VC-MRI. Note that the accuracy that can be achieved by VC-MRI is limited by the image resolution of the prior 4D MRI and on-board 2D cine MRI acquired. In our studies, both the prior 4D-MRI and on-board 2D cine MRI have a resolution of 1.875x1.875x3.000mm\(^3\) for XCAT data and 1.9x1.9x5.0mm\(^3\) for patient data. Therefore, we consider COMS within 2 mm as acceptable for VC-MRI estimation. VPD is sensitive to the target size and tends to be larger for smaller targets and smaller for larger targets, as it is calculated by dividing the target volume differences by the actual target volume size. Assuming the target volume is offset by 2 mm (the tolerance for COMS), the VPD for a 2 cm, 3 cm and

<table>
<thead>
<tr>
<th></th>
<th>Reference VC-MRI</th>
<th>Cartesian-based VC-MRI(_{acc})</th>
<th>Radial-based VC-MRI(_{acc})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.04±0.39</td>
<td>0.992</td>
<td>1.08±0.58</td>
</tr>
<tr>
<td></td>
<td>0.992</td>
<td>0.994</td>
<td>0.905</td>
</tr>
<tr>
<td></td>
<td>0.907</td>
<td>0.02±0.01</td>
<td>0.999</td>
</tr>
<tr>
<td>4</td>
<td>0.26±0.20</td>
<td>0.995</td>
<td>0.65±0.42</td>
</tr>
<tr>
<td></td>
<td>0.46±0.47</td>
<td>0.978</td>
<td>0.61±0.32</td>
</tr>
<tr>
<td></td>
<td>0.37±0.28</td>
<td>0.991</td>
<td>0.77±0.58</td>
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<td></td>
<td>0.921</td>
<td>0.921</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.30±0.30</td>
<td>0.924</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.27±0.29</td>
<td>0.938</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50±0.33</td>
<td>0.924</td>
</tr>
</tbody>
</table>
4 cm diameter target will be 28.9%, 19.4%, 14.2%, respectively, which were used as the tolerance for VPD in our studies.

6.1.4.1. Effects of Undersampling Acquisition Strategies

In the XCAT study, Cartesian sampling and radial sampling achieved accurate VC-MRI estimation when 10% and 5.2% of total k-space were sampled, respectively. For Cartesian based undersampling, sampling more signal in the central k-space, i.e. higher CP, led to better accuracy in the VC-MRI estimation. This can be explained by the fact that the central k-space region maintains the information about the gross anatomical structures of the patient, which are important for solving the PCA coefficients in the VC-MRI estimation. Additionally, it is important to note that sampling with a low SP but high CP is essentially similar to acquiring a lower resolution image. For the radial based undersampling, using golden angle distribution achieved slightly better accuracy than using even distribution.

In the patient study, using Cartesian-based undersampling produced accurate VC-MRI estimation when sampling 20% on Cartesian grid. Using radial-based sampling, VC-MRI estimation was accurate when using the golden angle with 32 spokes (SP=8%).

6.1.4.2. Effects of Tumor Size

In the XCAT study, VC-MRI estimation for a larger diameter tumor (40 mm diameter) resulted in accurate estimation when using the sagittal cine image acquired with 10% sampled k-space data, as shown in Table 16. When the XCAT tumor shrunk to
20 mm diameter, the VC-MRI estimation accuracy was reduced while still using 10% of total k-space for 2D cine image acquisition. Increasing with the sampling percentage to 20% of k-space improved the VC-MRI estimation accuracy for smaller tumors. This suggests that more k-space sampling is needed for smaller tumors in the VC-MRI estimation, mainly because there is less anatomical information in smaller tumors that can be used to determine the PCA coefficients. Also note that smaller tumors tend to lead to larger VPD values due to the sensitivity of VPD to the actual target volume.

Another solution for VC-MRI estimation with small tumors is to use higher spatial resolution 4D MRI and cine images. This is because more anatomical information is provided in the fine resolution images to solve for the PCA coefficients. In addition, it also improves the resolution of contouring the tumor volume, which is important for the accuracy of the VPD and COMS calculation for small tumors.

6.1.4.3. Clinical Relevance and Limitations

Using accelerated 2D cine images allows us to substantially improve the temporal resolution of the VC-MRI compared to using fully-sampled 2D cine images. This may improve moving target verification/tracking for patients with short or irregular breathing cycles. In addition, higher temporal resolution allows us to achieve better accuracy for post treatment accumulated dose evaluation and for deriving the tumor motion probability density function for probability-based treatments.[11] Using accelerated 2D cine images also makes it feasible to acquire multiple 2D cine images for
VC-MRI estimation to potentially improve the accuracy while maintaining a high temporal resolution. To give an example of this, an XCAT simulation was performed to investigate the effect of number of sagittal cine images on the accuracy of VC-MRI. Based on XCAT on-board scenario 2, when the number of 2D sagittal cine images increased from 1 to 10, the VPD/COMS for EOI phase improved from 9.33%/0.54mm to 4.76%/0.10mm based on Cartesian undersampling.

It is important to note that this study aimed to investigate the feasibility of using accelerated 2D cine images for VC-MRI estimation. Undersampling the k-space data is just one approach we explored for accelerating the 2D cine acquisition. There are other alternative methods, such as parallel imaging and reducing cine image resolution, which can also be used to accelerate 2D cine imaging for VC-MRI estimation. The efficacy of these alternative techniques for accelerating VC-MRI estimation will be investigated in future studies.

As stated above, in the current study, VC-MRI is estimated based on the 2D cine images reconstructed from the under sampled data. An alternative approach is to estimate VC-MRI directly from the undersampled k-space data, which can be computationally more efficient by skipping the 2D cine reconstruction process. However, it is challenging to implement this method based on the current VC-MRI estimation scheme. Due to the limitations of the motion model extracted by the PCA, VC-MRI estimation requires matching to an ROI around the target region in the image.
domain to account for day-to-day patient breathing variations, as demonstrated in our previous study [94]. This requirement cannot be satisfied when estimating VC-MRI directly from the k-space, since the signal from the ROI region in the image domain cannot be separated from signals in other regions in the k-space. The problem can potentially be resolved by developing an advanced motion modeling technique that models the relative organ motions in local regions to account for breathing variations. This method is still under development and further work is warranted.

The VC-MRI estimation has been evaluated by using both the 4D digital XCAT phantom and patient data in a retrospective approach in this study. The usage of XCAT provided several unique benefits: 1). Ground truth images are available for the evaluation of VC-MRI. 2). XCAT has the flexibility to simulate different patient breathing patterns, tumor sizes and noise levels to study their individual effects on the VC-MRI estimation so that VC-MRI can be better implemented for patient studies. The limitations of XCAT phantom are that they are simulated images with simplified anatomies. Future studies may incorporate more MR artifacts, such as ringing or blurring artifacts to make the images closer to clinical data. Additionally, undersampling artifacts were not simulated in the XCAT study, and future implementation of such artifacts would be beneficial.

In the retrospective patient study, the VC-MRI was evaluated using four liver cancer patients’ data. It is challenging to establish ground-truth images for patient
studies since currently there is no real time 3D MRI imaging technique available. In our study, tumor tracking curves extracted from orthogonal fully sampled 2D cine images were used as the references to evaluate the tumor tracking curves determined by the accelerated VC-MRI. Future studies may look into ways to better assess estimation accuracy in the retrospective study. For example, acquiring another 4D-MRI taken at a different time than prior 4D-MRI, and using the second 4D-MRI as the ground-truth to fully evaluate the accuracy of the VC-MRI in terms of tracking the tumor trajectory and reconstructing the 3D tumor volume. It is also worthy to mention that only retrospective patient data are included in the current study to evaluate the feasibility of accelerating the VC-MRI technique. Compared to prospective studies, retrospective studies have the advantages of providing the ground-truth images for evaluation and having the flexibility to investigate the effects of various under sampling strategies as well as various amounts of under sampling[101, 102, 106]. However, retrospective studies do not account for certain challenges in prospective in-vivo applications of the technique, such as undersampling artifacts, timing errors, gradient imperfections and Eddy currents in the MR acquisition. Therefore, future prospective patient studies are warranted to fully evaluate the VC-MRI technique for clinical applications. Challenges with establishing ground-truth images in the prospective studies need to be resolved before VC-MRI can be evaluated in the prospective study. Additionally, it is important to note that both the Cartesian and radial undersampled k-space data was
retrospectively generated by sampling the original fully-sampled Cartesian-based k-space data in the patient study. No radial k-space data were actually acquired. Radial k-space data generated from Cartesian k-space data may not be equivalent to the actual acquired radial k-space data, due to effects of gradient non-ideality, main field inhomogeneity and magnetic susceptibility. Because of this, radial k-space data will be acquired in the future prospective studies to further evaluate the accuracy of VC-MRI using radial undersampling.

Lastly, current processing time for VC-MRI estimation is ~2 minutes using in-house MATLAB programs, with ~1 minute to reconstruct the undersampled 2D cine images and ~1 minute to estimate the VC-MRI. Additional work is needed to accelerate the program using the graphics card, parallel computing or algorithm/code optimization to reduce the processing time to seconds to achieve real time 3D imaging with minimal latency time. Another point to make is that the VC-MRI estimation at different time steps are completely independent, and therefore they can be computed in parallel. During the implementation, although the calculation time causes a delay initially for generating VC-MRI at the first time step, VC-MRI at the following times steps will be generated continuously at the same temporal resolution as the accelerated 2D cine acquisition. Intrinsically, the generation of VC-MRI at all time steps has a latency period equal to the processing time. Acceleration strategies are being developed to reduce this intrinsic latency period from ~2 mins to seconds.
6.2. Improving VC-MRI Through Accelerated Multi-slice 2D Cine MRI Using Motion Modeling and Free-form Deformation

6.2.1. Background

A VC-MRI method was developed using a single 2D cine on-board MRI slice along with prior 4D MRI to estimate on-board 3D cine MRI for target localization, described in section 5.1. The method was accelerated using undersampled single 2D cine images to improve the temporal resolution of the VC-MRI, described in section 6.1. [95]. The original method used a motion model to estimate a deformation field map used to estimate the VC-MRI. This study aims to do the following: 1) introduce a free-form deformation model to correct for any errors in the motion modeling; 2) acquire multiple undersampled 2D cine images to provide adequate information for free-form deformation estimation while maintaining or improving the temporal resolution of the VC-MRI. The undersampled cine images will be reconstructed based on low-rank decomposition in the spatial-temporal domain [101]. This new VC-MRI method proposes to further improve the accuracy and temporal resolution of VC-MRI for different patient scenarios, making it a robust real-time 3D MR imaging technique. The method was evaluated using an anthropomorphic digital XCAT phantom.

6.2.2. Methods and Materials

Based on the previously developed method described in Section 5.1, the VC-MRI is estimated as follows [94, 95]. Prior 4D MRI is taken during simulation, and the end of
expiration (EOE) phase is designated as MRI\textsubscript{prior}. The on-board VC-MRI at each respiratory phase is considered a deformation MRI\textsubscript{prior}, shown in Equation 12.

\[ D \] is solved by using a motion modeling (MM) based optimization method. DFM\s are generated by deforming MRI\textsubscript{prior} to all other phases of the 4D MRI. PCA is used to extract out 3 major deformation modes from the DFM\s. Then, \( D \) can be represented as a weighted linear combination of the first three major deformation modes. The weighting coefficients can be solved for by using a data fidelity constraint, which matches the on-board 2D cine MRI to the corresponding slice of the VC-MRI. After the weighting coefficients are solved for, the final DFM can be calculated and VC-MRI can be generated by using Equation 12. For more details about the original VC-MRI method, refer Section 5.1.2.

\textbf{6.2.2.1. Free-form Deformation}

Anatomical changes from simulation to treatment may render the motion model inaccurate and affect the accuracy of the solved DFM. To solve these potential issues, a free-form deformation (FD) method is applied afterwards to fine tune the DFM. Without assuming any motion models, the FD method allows each voxel in the DFM to move freely with the constraint of energy minimization to preserve the smoothness of \( D \). The energy of the DFM is defined in Equation 5.
The goal of the free-form deformation optimization is to find the DFM satisfying Equation 7, subject to the new data fidelity constraint in Equation 19, which matches the on-board 2D cine MRI with the corresponding slice of the VC-MRI.

\[ f(D) = \sum_i \left\| S_i \ast \text{VCMRI}(\text{MRI prior}, D) - 2\text{DCine}_i \right\|^2_2 \leq \epsilon \quad (19) \]

Here, \( i \) represents the sum over the multiple cine slices. The energy constraint and the data fidelity constraint are enforced consecutively through gradient descent optimization to adaptively control the step size to reach final convergence.

### 6.2.2.2. Multi-slice Undersampled 2D Cine MRI Using k-t SLR Reconstruction

Free-form deformation estimation requires the use of multiple on-board 2D images in the data fidelity constraint due to its large number of variables. Using undersampled 2D cine MRI allows for acceleration to acquire multiple 2D cine images for VC-MRI estimation without sacrificing its temporal resolution. A previously developed low-rank decomposition method was used to reconstruct the undersampled cine images [101]. The low-rank decomposition method uses k-t SLR to reconstruct highly undersampled 2D cine images, utilizing both spatial and temporal information. The main optimization equation used to reconstruct the undersampled k-space data is shown in Equation 20.

\[ \arg\min_x \left\| F_p(X) - k \right\|^2 + \lambda_1 \phi(X) + \lambda_2 \text{TV}(X) \quad (20) \]

The images were assumed rank deficient, and so the sparse vector \( x \) can be generalized to a low-rank matrix, \( X \). \( F_p \) is the partial Fourier transformation, \( k \) is the
undersampled k-space data, $\lambda_1$ and $\lambda_2$ are regularization parameters. A TV constraint in both the spatial and temporal domain was used to exploit the sparse gradients of the dynamic images. Equation 20 is named as k-t SLR. Additional details of the reconstruction algorithm can be found in [101, 107]. The k-t SLR produces high quality reconstructed images based on highly undersampled k-space data due to the decomposition in the spatial-temporal domain by better using the anatomical coherence from the images.

The image size was 256 x 256 with 21 time-steps. Fully sampled k-space data was defined as sampling 256 phase-encoded lines. In this study, 10% of fully sampled k-space data was acquired on a Cartesian coordinate system. Of the 10% of the undersampled data, 10% of that was acquired uniformly in the center k-space. The rest of k-space was randomly sampled. Each of the 21 time-step slices had a different random phase-encoded lines sampled.

6.2.2.3. XCAT Simulation

A digital anthropomorphic phantom, XCAT, was used to simulate the prior 4D MRI and ground-truth on-board 4D MRI [108]. The respiratory motion for the phantom was controlled by two respiratory curves: the diaphragm curve and the chest wall curve. The diaphragm curve mainly determines the motion in the superior-inferior (SI) direction, and the chest wall curve mainly controls the motion in the anterior-posterior (AP) direction. No lateral motion was simulated.
6.2.2.3.1. Prior 4D MRI Simulation

A spherical lesion of 30 mm diameter was simulated in the middle of the lung in XCAT. The respiratory cycle was set to 5 second, and the peak-to-peak amplitudes of the diaphragm curve and chest wall curve were set to 3 and 2 cm, respectively. A ten-phase 4D MRI was then simulated as the prior 4D MRI. The MRI volume of each phase was composed of 256 x 256 x 100 voxels, with each voxel measuring 1.875x1.875x3mm$^3$ in dimension. The XCAT phantom was generated in activity mode in order to produce MRI-like images.

6.2.2.3.2. Ground-truth VC-MRI Simulation

Based on parameters used to generate the prior 4D MRI, eight patient scenarios were simulated for on-board volume sets to reflect different on-board respiratory and anatomical changes.

(1) Diaphragm curve and chest wall curve were set to 2 cm and 1.2 cm, respectively. (2) Based on scenario 1, also with tumor diameter decreased to 25 mm. (3) Based on scenario 1, also with tumor diameter increased to 40 mm. (4) Based on scenario 1, also with tumor average position shifted in SI direction by 8 mm. (5) Based on scenario 1, also with tumor average position shifted in AP direction by 8 mm. (6) Based on scenario 1, also with tumor average position shifted in SI, AP and lateral directions by 5 mm each. (7) Based on scenario 1, also with tumor having 20% phase shift relative to body. (8) Diaphragm curve and chest wall curve for body volume set to 2 cm and 1.2
cm, respectively. Diaphragm curve and chest wall curve for tumor volume set to 4 cm and 3 cm, respectively.

### 6.2.2.3. On-board 2D Cine MR Simulation

2D sagittal, axial and coronal slices were extracted from the ground-truth VC-MRI at various locations through and around the tumor in the MRI$_{prior}$ volumes to simulate on-board 2D cine MRI. The direct Fourier transform of each slice was taken to simulate fully sampled k-space. Then, the k-space data was undersampled and reconstructed based on k-t SLR described in section 6.2.2.2.

### 6.2.2.4. Effect of Region of Interest (ROI) Selection

In the original VC-MRI method, estimation using an ROI around the tumor of a sagittal 2D cine image resulted in the most accurate VC-MRI estimation compared to matching to the entire cine image [94]. For this study, the following regions were used for matching in the MM-FD algorithm. (1) Global MM only. (2) ROI MM only. (3) Global MM with Global FD. (4) Global MM with ROI FD. (5) ROI MM with Global FD. (6) ROI MM with ROI FD.

### 6.2.2.5. Effect of Slice Orientation, Slice Number and Slice Location

To evaluate the effect slice orientation, sagittal, coronal and axial slices were extracted. The following orientations were investigated. (1) Multiple sagittal slices. (2) Multiple axial slices. (3) Multiple coronal slices. (4) Sagittal, axial and coronal orthogonal slices.
To evaluate the effect of slice number, the following various slice numbers were investigated. (1) 30 sagittal slices. (2) 15 sagittal slices. (3) 10 sagittal slices. (4) 20 axial slices. (5) 10 axial slices. (6) 30 coronal slices. (7) 15 coronal slices. (8) 10 coronal slices. (9) 30 orthogonal slices: 10 axial, 10 sagittal, 10 coronal. (10) 15 orthogonal slices: 5 axial, 5 sagittal, 5 coronal. The difference in number of sagittal and coronal slices compared with axial slices is due to the fact that the SI direction of the images had a courser resolution. Figure 28a) shows the slice distribution of the 30, 15 and 10 uniformly distributed sagittal slices for a visual reference.

Different slice locations were extracted to evaluate the effect of slice location compared to VC-MRI estimation accuracy. Slices were uniformly taken throughout all locations of the tumor in the MRI_{prior} volume, with slices extracted out to xx mm, xx mm and xx mm in the SI, AP and lateral directions surrounding the tumor. To evaluate the effect of slice location on the VC-MRI estimation accuracy, 10 sagittal slices were extracted in the following locations: (1) slices distributed non-uniformly with a much higher density taken in the center of the tumor and only two slices extracted from the periphery (2) high density of slices extracted in periphery and high density of slices extracted in center and (3) higher density of slices extracted through periphery of tumor with one slice extracted from center. Figure 28b) shows the slice distribution for the 3 slice locations described.
6.2.2.6. Evaluation Methods

The estimation accuracy for tumor location and volume in the VC-MRI was evaluated at EOI phase since it has the largest deformation from MRIprior. Tumors were automatically contoured in an in-house MATLAB (MathWorks, Natick, MA) code based on a threshold voxel value in both the estimated images and the ground-truth images for comparison. Three metrics were defined to quantify the accuracy of the estimated tumor volume: volume percent difference (VPD), volume dice coefficient (VDC), and center-of-mass shift (COMS) shown in Equations 10, 11 and 16 [94, 109]. Image profiles were also generated.
6.2.3. Results

6.2.3.1. Undersampled Cine MRI using k-t SLR Reconstruction

Figure 29 shows end-inspiration time-step images from axial, coronal and sagittal cine images using full sampled k-space, undersampled k-space with the k-t SLR reconstruction method and undersampled k-space using the TGV reconstruction method used in Section 6.1.2. Both the k-t SLR and TGV reconstruction images were reconstructed using 10% of total k-space sampled.

![Figure 29](image)

Figure 29: End-inspiration time-step images from axial, coronal and sagittal cine images using full sampled k-space, undersampled k-space with the k-t SLR reconstruction method and undersampled k-space using the TGV reconstruction method used in Section 6.1.2.
6.2.3.2. Effect of Region of Interest (ROI) Selection

Table 18 shows VPD, VDC and COMS for all XCAT scenarios comparing global MM with ROI MM.

**Table 18: VPD, VDC and COMS for all XCAT scenarios comparing global MM and ROI MM.**

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td>GMM</td>
<td>15.56</td>
<td>69.39</td>
<td>58.22</td>
<td>81.49</td>
<td>68.76</td>
<td>89.96</td>
<td>8.13</td>
</tr>
<tr>
<td></td>
<td>ROIIM</td>
<td>8.57</td>
<td>31.12</td>
<td>42.06</td>
<td>31.40</td>
<td>12.44</td>
<td>35.88</td>
<td>8.63</td>
</tr>
<tr>
<td>VDC</td>
<td>GMM</td>
<td>0.92</td>
<td>0.77</td>
<td>0.60</td>
<td>0.58</td>
<td>0.65</td>
<td>0.54</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>ROIIM</td>
<td>0.96</td>
<td>0.86</td>
<td>0.73</td>
<td>0.84</td>
<td>0.94</td>
<td>0.81</td>
<td>0.96</td>
</tr>
<tr>
<td>COMS(mm)</td>
<td>GMM</td>
<td>1.45</td>
<td>1.59</td>
<td>1.41</td>
<td>8.88</td>
<td>7.75</td>
<td>9.83</td>
<td>0.56</td>
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<tr>
<td></td>
<td>ROIIM</td>
<td>0.32</td>
<td>1.3</td>
<td>2.38</td>
<td>3.07</td>
<td>0.23</td>
<td>3.93</td>
<td>0.18</td>
</tr>
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</table>

Table 19 shows VPD, VDC and COMS for all XCAT scenarios comparing global FD with ROI FD. For both global MM and ROI MM, global FD and ROI FD was done to test the effect of ROI section on the free-form deformation optimization. Figure 30 shows MRI\textsubscript{prior}, ground truth VC-MRI (VCMRI\textsubscript{GT}) and estimated VC-MRI (VCMRI\textsubscript{Est}) using ROIMM-ROI FD estimation, along with the corresponding profile curves for XCAT scenario 2. Figure 31 shows the corresponding subtraction images for figure 30.

**Table 19: VPD, VDC and COMS for all XCAT scenarios comparing global FD and ROI FD.**

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>VPD(%)</td>
<td>GMMGFD</td>
<td>0.63</td>
<td>1.16</td>
<td>11.07</td>
<td>11.94</td>
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<td>GMMROIFD</td>
<td>0.95</td>
<td>1.27</td>
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<td>7.94</td>
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<td></td>
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<td>ROIMMROIFD</td>
<td>VDC</td>
<td>GMMGFD</td>
<td>GMMROIFD</td>
<td>ROIMMGFD</td>
<td>ROIMMROIFD</td>
<td>COMS(mm)</td>
</tr>
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<tr>
<td></td>
<td>0.57</td>
<td>0.76</td>
<td>1.00</td>
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<td>1.05</td>
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<td>5.31</td>
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<td>2.34</td>
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<td>0.94</td>
<td>0.98</td>
<td>0.97</td>
<td>0.28</td>
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<td>0.99</td>
<td>0.05</td>
<td>1.41</td>
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<tr>
<td></td>
<td>1.33</td>
<td>1.20</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.10</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>1.32</td>
<td>3.02</td>
<td>0.99</td>
<td>0.96</td>
<td>0.96</td>
<td>0.99</td>
<td>0.29</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>4.54</td>
<td>4.54</td>
<td>0.88</td>
<td>0.96</td>
<td>0.98</td>
<td>0.98</td>
<td>0.29</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**Figure 30:** MRI<sub>Prior</sub>, ground truth VC-MRI (VCMRI<sub>GT</sub>) and estimated VC-MRI (VCMRI<sub>Est</sub>) using ROIMM-ROIFD estimation, along with the corresponding profile curves for XCAT scenario 2.
6.2.3.3. Effect of Acquisition Orientation

Table 20 shows VPD, VDC and COMS for all XCAT scenarios comparing different orientation and slice numbers. Sagittal, axial and coronal cine images were used to evaluate the effect of acquisition orientation. Orthogonal cine images were also
used, which consisted of equal numbers of sagittal, axial and coronal cine images. For sagittal and coronal cine images, 30 15 and 10 slices were used. For axial images, 20 and 10 slices were used. This was due to the fact that the resolution in the out-of-plane direction was coarser than the resolution in the in-plane direction. For the orthogonal orientation, 30 and 15 total slices were investigated. For the 30 orthogonal slices, 10 sagittal, 10 coronal and 10 axial images were used. For the 15 total slices, 5 sagittal, 5 coronal and 5 axial images were used.

Table 20: VPD, VDC, COMS for all XCAT scenarios comparing different acquisition orientations and slice numbers.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPD(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Sagittal</td>
<td>0.76</td>
<td>1.48</td>
<td>0.66</td>
<td>3.35</td>
<td>0.63</td>
<td>1.20</td>
<td>3.02</td>
<td>4.54</td>
</tr>
<tr>
<td>30 Coronal</td>
<td>3.78</td>
<td>6.54</td>
<td>8.70</td>
<td>6.57</td>
<td>3.75</td>
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<td>10 Sagittal</td>
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<td>18.63</td>
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<td>29.84</td>
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<td>20.66</td>
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<tr>
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<td>0.93</td>
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<tr>
<td>30 Ortho</td>
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<tr>
<td>15 Sagittal</td>
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<tr>
<td>15 Coronal</td>
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<td>0.95</td>
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<td>0.95</td>
<td>0.92</td>
<td>0.97</td>
<td>0.88</td>
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</table>
Table 21 shows VPD, VDC and COMS for all XCAT scenarios comparing different slice locations. For each of the estimation results, 10 sagittal cine images were used. ‘Uniform’ refers to evenly distributed slices. ‘Non-uniform1’ refers to slices distributed non-uniformly with a much higher density taken in the center of the tumor and only two slices extracted from the periphery (bottom left image in Figure 28b). ‘Non-uniform2’ refers to high density of slices extracted in periphery and high density of slices extracted in center (bottom middle image in Figure 28b), and ‘Non-uniform3’ refers to higher density of slices extracted through periphery of tumor with one slice extracted from center (bottom right image in Figure 28b).
Table 21: VPD, VDC and COMS for different slice locations.

<table>
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<tr>
<th>Scenarios</th>
<th>1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<th>8</th>
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<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Uniform</td>
<td>7.62</td>
<td>8.23</td>
<td>18.63</td>
<td>7.64</td>
<td>7.37</td>
<td>9.73</td>
<td>9.07</td>
<td>9.89</td>
</tr>
<tr>
<td>Non-uniform1</td>
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<td>12.87</td>
<td>28.60</td>
<td>7.20</td>
<td>6.73</td>
<td>25.39</td>
<td>9.26</td>
<td>11.91</td>
</tr>
<tr>
<td>Non-uniform2</td>
<td>11.66</td>
<td>37.03</td>
<td>38.98</td>
<td>13.71</td>
<td>13.52</td>
<td>43.08</td>
<td>8.13</td>
<td>20.23</td>
</tr>
<tr>
<td>Non-uniform3</td>
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<td>29.81</td>
<td>16.68</td>
<td>10.10</td>
<td>28.74</td>
<td>8.07</td>
<td>22.24</td>
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<tr>
<td>VDC</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform</td>
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<td>0.90</td>
<td>0.96</td>
<td>0.96</td>
<td>0.95</td>
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<td>0.76</td>
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<td>0.93</td>
<td>0.78</td>
<td>0.96</td>
<td>0.90</td>
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<tr>
<td>Non-uniform3</td>
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<td>0.82</td>
<td>0.92</td>
<td>0.95</td>
<td>0.86</td>
<td>0.96</td>
<td>0.89</td>
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<tr>
<td>COMS(mm)</td>
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<td></td>
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<tr>
<td>Uniform</td>
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<td>1.29</td>
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<td>0.58</td>
<td>0.89</td>
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<tr>
<td>Non-uniform1</td>
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<td>0.64</td>
<td>0.73</td>
<td>0.44</td>
<td>3.13</td>
<td>0.67</td>
<td>1.24</td>
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<tr>
<td>Non-uniform2</td>
<td>0.85</td>
<td>1.19</td>
<td>0.58</td>
<td>1.24</td>
<td>0.50</td>
<td>4.98</td>
<td>0.32</td>
<td>1.84</td>
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<tr>
<td>Non-uniform3</td>
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<td>1.47</td>
<td>1.65</td>
<td>0.54</td>
<td>2.08</td>
<td>0.23</td>
<td>2.22</td>
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</tbody>
</table>

6.2.4. Discussion

The VC-MRI generation method using multiple undersampled 2D cine images, motion modeling and free-form deformation can substantially improve the VC-MRI accuracy from the previous methods developed in Section 5.1 and 6.1. This new method introduces free-form deformation models to correct for any errors in the motion modeling, and it acquires multiple undersampled 2D cine images to provide adequate information for the free-form deformation estimation while maintaining the temporal
resolution of the VC-MRI. The innovate k-t SLR reconstruction algorithm used to reconstruct the undersampled 2D cine k-space data used the spatio-temporal information of the data to reconstruct high quality cine images, while only acquiring 10% of total k-space.

Results shown in Section 6.2.3.3. showed that acquiring multiple sagittal cine images provided better VC-MRI estimation than acquiring multiple axial, coronal or orthogonal cine images. The more sagittal slices, the higher the VC-MRI accuracy, however, using 10 sagittal slices provided adequate VC-MRI accuracy across all 8 XCAT scenarios. Using 10 cine slices, undersampled with each slice acquiring 10% of total k-space data, results in a maintained temporal resolution of VC-MRI when compared to using a single fully-sampled cine image.

Based on results shown in Table 18, acquiring the multiple slices uniformly across the tumor region resulted in better accuracy than acquiring the slices non-uniformly distributed throughout the tumor region.

The work described in Section 6.2. consists of using XCAT simulation data only. While the analysis with XCAT data was robust, future work should be done to test the method using patient data. A prospective study should be implemented to acquire multiple 2D cine images using only 10% of k-space data with many liver patients.

In general, this new method further improves the accuracy of VC-MRI for different patient scenarios, making it a robust real-time volumetric MRI technique.
These improvements of delivery accuracy can potentially improve the treatment outcome and pave the road to further margin reduction and dose escalation.

7. Conclusions and Future Directions

The goal of this dissertation work is to develop novel techniques to generate real-time volumetric imaging for target localization during IGRT. The work presented in this dissertation uses prior 4D patient information, limited on-board data and deformation models to estimate real-time volumetric imaging for on-board target localization in radiation therapy.

First, a quasi-cine CBCT estimation technique was generated to estimated 4D CBCT using prior 4D CT and extremely limited angle on-board projections. This worked aimed to improve a previously developed MM-FD method, which generated accurate 4D CBCT estimation using orthogonal-view 30° scan angles. The improved CBCT estimation technique uses a structural-based PCA motion modeling algorithm and a weighted free-form deformation technique to estimated 4D CBCT using orthogonal-view 15° scan angles. The structural-based PCA motion modeling decouples the correlation between motion patterns of different anatomical structure and allows relative motion between anatomical structures to change from CT to CBCT, which is more clinically realistic. The weighted free form deformation gives extra freedom for adjusting weightings of different regions in the data fidelity constraint to optimize the image estimation accuracy of the region of most clinical interest. The structural based
PCA motion modeling along with the weighted free-form deformation methods improved the accuracy of the 4D CBCT estimation substantially, especially when using extremely small scan angles or low number of projections. This results in lower imaging dose and time, which will lead us to achieve ultra-fast 4D CBCT imaging for either inter- or intra-fraction verification to improve the treatment accuracy.

The rest of the dissertation work aim to develop novel methods to generate cine 3D or 4D MRI for on-board MRI-guided radiation therapy. A technique was developed to generate real-time volumetric cine MRI using prior 4D MRI, a single on-board 2D cine MRI and motion modeling. Different from 2D cine MRI and 4D-MRI, VC-MRI can potentially achieve both high temporal and spatial resolution depending on the quality of the prior images. VC-MRI allows for the first time to localize the full 3D target volume continuously in real time to improve the localization accuracy of SBRT both before and during the actual treatment. The real time volumetric localization by VC-MRI also makes it feasible to perform real time 4D gating or target tracking during treatments.

Then, a technique was developed to estimate on-board 4D MRI using prior 4D MRI and limited angle kV projections from a conventional LINAC. MRI-radiotherapy units are only available in a limited number of clinics, but this technique is applicable in all LINACs with kV imaging capabilities, and can significantly enhance the applications of MRgRT in clinics, especially for liver SBRT treatments. The MR guidance provided by this technique can potentially improve the localization accuracy of liver SBRT, which can
lead to better tumor control and lower toxicities paving the road to further margin reduction and dose escalation.

Lastly, acceleration and improved accuracy of VC-MRI were investigated. VC-MRI was accelerated by using undersampled 2D cine MRI in the estimation algorithm. Using accelerated 2D cine images allows us to substantially improve the temporal resolution of the VC-MRI compared to using fully-sampled 2D cine images. This may improve moving target verification/tracking for patients with short or irregular breathing cycles. In addition, higher temporal resolution allows us to achieve better accuracy for post treatment accumulated dose evaluation and for deriving the tumor motion probability density function for probability-based treatments.

VC-MRI accuracy was improved by using multiple undersampled 2D cine images and introducing a free-form deformation to fine-tune the DFM solved by the motion modeling method. This new VC-MRI estimation method improves the accuracy of VC-MRI for different patient scenarios, making it a robust real-time volumetric MRI technique.

Future directions of the work presented in this dissertation may include more patient studies to further evaluate the methods developed in this dissertation. Many of the studies were only evaluated with a limited number of patient data, and a future clinical trial to investigate the clinical feasibility of the methods developed in this dissertation are warranted.
Additional modeling may be implemented into the VC-MRI techniques to further improve the estimation. Furthermore, the volumetric cine imaging techniques developed can potentially be used for intra-fraction real time 3D motion prediction. A newly published prediction method was generated to predict respiratory motion for lung cancer patients [110]. A future study may be done to use this prediction method, along with the VC-MRI techniques developed in this dissertation to predict real time volumetric deformations for real time 3D target tracking. The predicted deformation can also potentially improve the VC-MRI estimation accuracy at the next time step by providing a better starting point in the optimization algorithm.
References


[44] D. Staub, A. Docef, R.S. Brock, C. Vaman, M.J. Murphy, 4D Cone-beam CT reconstruction using a motion model based on principal component analysis, Medical physics, 38 (2011) 6697-6709.


Biography

Wendy Beth Harris was born on May 14th, 1990 in Summit, New Jersey. In 2008, she began her undergraduate education at Drexel University in Philadelphia, Pennsylvania. She graduated from Drexel University in June 2013 with a Bachelor of Science in Physics and a Minor in Mathematics. In August 2013, she entered the Duke University Medical Physics Graduate Program, where she began working towards her Doctor of Philosophy under the advisement of Dr. Lei Ren and Dr. Fang-Fang Yin.

During her time at Duke University, she has received many honors and awards, such as a conference travel award from the Duke University Graduate School, the James T. Dobbins III Leadership Award from the Duke University Medical Physics Graduate Program, and she was a co-author on the Innovation in Medical Physics Education Award from the American Association of Physicists in Medicine (AAPM). Wendy Harris also has first author publications in the International Journal of Radiation Oncology Biology Physics, Medical Physics and Physics in Medicine and Biology. She has presented her research both nationally, at the AAPM Annual Meetings, and internationally, at the International Society of Magnetic Resonance in Medicine Annual Meeting.