Development and Optimization of Four-dimensional Magnetic Resonance Imaging (4D-MRI) for Radiation Therapy

by

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Medical Physics Graduate Program
Duke University

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Bastiaan Driehuys, Supervisor

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Nan-kuei Chen

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Brian G. 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

A tenet of modern radiotherapy (RT) is to identify the treatment target accurately, following which the high-dose treatment volume may be expanded into the surrounding tissues in order to create the clinical and planning target volumes. Respiratory motion can induce errors in target volume delineation and dose delivery in radiation therapy for thoracic and abdominal cancers. Historically, radiotherapy treatment planning in the thoracic and abdominal regions has used 2D or 3D images acquired under un-coached free-breathing conditions, irrespective of whether the target tumor is moving or not. Once the gross target volume has been delineated, standard margins are commonly added in order to account for motion. However, the generic margins do not usually take the target motion trajectory into consideration. That may lead to under- or over-estimate motion with subsequent risk of missing the target during treatment or irradiating excessive normal tissue. That introduces systematic errors into treatment planning and delivery. In clinical practice, four-dimensional (4D) imaging has been popular in RT motion management. It provides temporal information about tumor and organ at risk motion, and it permits patient-specific treatment planning. The most common contemporary imaging technique for identifying tumor motion is 4D computed tomography (4D-CT). However, CT has poor soft tissue contrast and it induce ionizing radiation hazard. In the last decade, 4D magnetic resonance imaging (4D-MRI) has become an emerging tool to image respiratory motion, especially in the abdomen, because of the superior soft-tissue contrast. Recently, several 4D-MRI techniques have been proposed, including prospective and retrospective approaches. Nevertheless, 4D-MRI techniques are faced with several challenges: 1) suboptimal and inconsistent tumor contrast with large inter-patient variation; 2) relatively low temporal-spatial resolution; 3) it lacks a reliable respiratory surrogate. In this research work, novel 4D-MRI
techniques applying MRI weightings that was not used in existing 4D-MRI techniques, including T2/T1-weighted, T2-weighted and Diffusion-weighted MRI were investigated. A result-driven phase retrospective sorting method was proposed, and it was applied to image space as well as k-space of MR imaging. Novel image-based respiratory surrogates were developed, improved and evaluated.
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Chapter 1: Introduction

1.1 Statement of problem

A tenet of modern radiotherapy (RT) is to identify the treatment target accurately, following which the high-dose treatment volume may be expanded into the surrounding tissues in order to create the clinical and planning target volumes. Respiratory motion can induce errors in target volume delineation and dose delivery in radiation therapy for thoracic and abdominal cancers. Historically, radiotherapy treatment planning in the thoracic and abdominal regions has used 2D or 3D images acquired under un-coached free-breathing conditions, irrespective of whether the target tumor is moving or not. Once the gross target volume has been delineated, standard margins are commonly added in order to account for motion. However, the generic margins do not usually take the target motion trajectory into consideration. That may lead to under- or over-estimate motion with subsequent risk of missing the target during treatment or irradiating excessive normal tissue. That introduces systematic errors into treatment planning and delivery. In clinical practice, four-dimensional (4D) imaging has been popular in RT motion management. It provides temporal information about tumor and organ at risk motion, and it permits patient-specific treatment planning. The most common contemporary imaging technique for identifying tumor motion is 4D computed tomography (4D-CT). It has been widely used to image subject-specific respiratory motion for determining internal target volumes (ITVs) and individual safety margins. However, its application in abdominal cancers has been largely limited due to low soft tissue contrast. In addition, 4D-CT involves high imaging radiation dose to the human subjects. Recently, several 4D magnetic resonance imaging (4D-MRI) techniques have been proposed in order to overcome the limitations of 4D-CT. 4D-MRI yields no radiation
dose to human subjects and can provide improved soft-tissue contrast without significantly adding imaging time and cost \(^1,10-12\).

At the time when I started my research, several methods of 4D-MRI had been proposed. In brief, there were two main approaches to develop 4D-MRI: (1) prospective 4D-MRI, which used fast 3D MR sequences to acquire real-time volumetric images or fast 2D MRI acquisition with respiratory gating. Due to current technical limitations, significant compromise on image quality had to be made in order to achieve the high speed of 3D MR imaging. For example, Dinkel et al developed a real-time MRI using 4D FLASH with TREAT technique. It was a T1-weighted MRI sequence with temporal and spatial resolutions of approximately 1 s and 4 mm \(^14\), respectively, inadequate for radiotherapy applications. Blackall et al implemented a T1-weighted 3D real-time MRI using Fast Field Echo-Echo Planar Imaging (FFE-EPI) sequence with sensitivity encoding (SENSE) technique \(^15\). It achieved a high frame rate (330 ms/volume) and spatial resolution (1.8×1.8×7 mm). However, significant compromises in image quality had to be made to achieve real-time imaging, resulted in inadequate image quality for RT application. Hu et al developed a prospective T2-weighted 4D-MRI technique with a respiratory amplitude based triggering system to gate 2D MRI image acquisition \(^9\). In addition, Akçakaya et al developed a T1-weighted 4D-MRI k-space-dependent respiratory gating technique. With this technique, a respiratory navigator was used as the surrogate to gate the acquisition of the k-space center data \(^47\). Both 4D-MRI techniques using 3D MRI sequences and 2D MRI sequences acquired data only when respiratory motion reaches pre-set motion amplitude using prospective gating. However, the 4D-MRI using gating technique leading to a longer image acquisition time, which was suboptimal for RT application; (2) retrospective 4D-MRI, which used fast 2D MR sequences to continuously acquire images for volume of interest under free
breathing condition. 2D MRI images of different respiratory phases at all slice locations were acquired. Subsequently, the 2D MRI images were sorted and re-binned based on the corresponding respiratory amplitudes or phases, which was calculated from synchronized motion signal \(^{13,59}\). For example, Cai et al proposed a T2/T1-weighted \(^{77}\) 4D-MRI phase sorting technique that used body area (BA) extracting from images as the respiratory surrogate for sorting \(^{13,38}\). In summary, 4D-MRI techniques developed so far have utilized both prospective and retrospective approaches and had utilized different contrast mechanisms (T1- and T2/T1-weighted). Because of the disadvantages described above about prospective approach, we focus on further development of retrospective 4D-MRI techniques in our study.

1.2 Challenge

The retrospective 4D-MRI techniques introduced above had been shown to be promising in achieving high soft-tissue contrast and image spatial and/or temporal resolutions. However, from the limited number of patient studies of these techniques \(^{13,16,38}\), it has been observed that current 4D-MRI techniques were faced with several important challenges: (1) the 4D-MRI images suffered from inconsistent or insufficient tumor-to-tissue contrast for RT applications. For example, Cai et al used T2/T1-weighted \(^{77}\) MRI sequence for 4D-MRI development. We measured the tumor contrast-to-noise ratio (CNR) of MRI images with T2/T1-weighted signal for 10 liver cancer patients, as shown in Table. 1. CNR varies largely between different patients. Besides, T2/T1-weighted MRI does not provide the most optimal contrast for abdominal organs. There are other MRI signals weighting mechanisms that can provide better tumor contrast. For example, T2-weighted MRI is the clinical standard MR sequence for liver cancer diagnosis,
often presenting higher tumor contrast than what can be provided by the developed 4D-MRI techniques. Furthermore, Diffusion-weighted imaging (DWI) is increasingly being used in clinical applications. It offers anatomical and functional information with excellent tumor-tissue contrast that can be used in conjunction with other imaging modalities to help with diagnosis disease, treatment planning and assessing/monitoring of tumor treatment success. Both of the two MRI weightings have higher clinical diagnosis value and worth to be investigated for 4D-MRI development. These MRI sequences have different image acquisition mode than the developed 4D-MRI techniques and 4D-CT. Hence, novel sorting and reconstruction techniques regarding these MRI sequences providing new 4D-MRI weightings could be desirable; (2) the existing sorting method for retrospective 4D-MRI techniques are not optimal. The image-based sorting methods have a pre-request of high 2D MRI image acquisition frame rate (frame rate > 2 f/s). The image acquisition time for each 2D MRI image should be short enough so that each image slice is not blurred by the respiratory motion. With fast image acquisition, the 2D MRI image quality is sacrificed. In other words, applying MRI sequence for 4D-MRI development requires a balance between temporal resolution and 2D MRI image quality. Besides, there are several MRI sequences which provide excellent tumor contrast but do not even meet the frame rate requirement. For example, T2-weighted MRI sequence fast recovery fast spin echo (FRFSE) is the standard sequence for abdominal imaging. It provides excellent tumor contrast for liver and other abdominal organs. However, its frame rate is about 0.5 frames/s, much lower than the frame rate pre-request of image-based retrospective 4D-MRI sorting. The high frame rate requirement limits the improvement of 2D MRI image quality, and thus limits the best image quality we can achieve for 4D-MRI; (3) 4D-MRI techniques are in lack of a reliable and clinically practical respiratory surrogates for 4D-MRI technique. Retrospective 4D-MRI techniques
continually acquire 2D MR image data during free breathing and then sort the images based on the corresponding respiratory status. As an indication of respiratory motion status, respiratory motion is simultaneously recorded with respiratory surrogate during image acquisition. The synchronized motion signal is used to determine the respiratory phase at each image acquisition time for sorting purpose. Tryggestad et al developed a retrospective 4D-MRI technique using an external respiratory surrogate Physiologic Monitoring Unit (PMU) with a pneumatic device Velcro-strapped around the subjects’ upper abdomen. The external surrogate requires extra pre-scan set up of the monitor device, making it inconvenient and costly for 4D-MRI application. Siebenthal et al developed a method using an MR navigator for retrospectively stacking dynamic 2D images to generate time-resolved 3D images. However, there is a time interval between the navigator image acquisition time and the data image acquisition time, leading to un-synchronized respiratory signal with MRI image. Internal surrogate is another option that can be considered for 4D-MRI. However, the surgical procedure for the internal markers implantation can be unsafe for the patient. The markers can also migrate, decreasing the correlation between the marker and the tumor's motion. The unreliability of internal respiratory surrogates and inconvenience of external respiratory surrogates largely influence the image quality of 4D-MRI, hence limit their implementation in RT. Improvement and development of a reliable and clinical practical respiratory surrogate are necessary.

Table 1. Summary of patients’ characteristics and CNR measurements on T2/T1 MRI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Cancer site</th>
<th>CNR T2/T1 MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>F</td>
<td>HCC</td>
<td>4.57</td>
</tr>
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<td>2</td>
<td>65</td>
<td>M</td>
<td>Liver Mets</td>
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<tr>
<td>3</td>
<td>61</td>
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<td>HCC</td>
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<tr>
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<td>M</td>
<td>HCC</td>
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<td>35</td>
<td>F</td>
<td>Liver Mets</td>
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<td>M</td>
<td>HCC</td>
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<td>F</td>
<td>HCC</td>
<td>5.98</td>
</tr>
<tr>
<td>Mean</td>
<td>63</td>
<td>/</td>
<td>/</td>
<td>9.92</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(±12)</td>
<td>/</td>
<td>/</td>
<td>(±12.9)</td>
</tr>
</tbody>
</table>

Abbreviations: F: female; M: male; SD: standard deviation; CNR: contrast-to-noise ratio; MRI: magnetic resonance imaging. HCC: Hepatocellular carcinoma; Liver Mets: liver metastasis.

1.3 Objective

This dissertation projects sought to address the challenges that are mentioned above to improve 4D-MRI for radiation therapy. The specific aims are listed below. They cover the explorations of improvements I tried to achieve for 4D-MRI, aiming at addressing the problems 4D-MRI techniques are faced with. Innovation in this proposal is evident in the topic of the concepts and the implementation of approaches. Result-driven phase sorting is a novel concept. It is applied to image space as well as k-space of MR imaging. Although phase sorting has been widely used in 4D imaging reconstruction, sorting method that utilize both phase information and relative amplitude information have not yet been developed. This new concept will provide guidance on how to deal with redundant images acquired during 4D-MRI scanning. The proposed 4D MR imaging using different MRI weightings, including T2/T1, T2 and diffusion are novel techniques. 4D-MRI with these signal weightings may provide better tumor-to-tissue contrast than other developed 4D-MRI techniques. The proposed image-based respiratory surrogates are novel developments. The exploration and estimation of these surrogates
provided us better understanding on the characteristics of respiratory surrogates that are necessary for 4D-MRI sorting.

1.3.1. Specific aims

Aim 1: To further develop image-based retrospective 4D-MRI technique

- Aim 1a: To improve the 4D-MRI technique based on body-area surrogate using cine sagittal image acquisition
- Aim 1b: To investigate the sagittal-coronal-diaphragm point of intersection (SCD-PoI) as respiratory surrogate for retrospective 4D-MRI
- Aim 1c: To develop and evaluate a T2-weighted retrospective 4D-MRI technique using sequential image acquisition

Aim 2: To develop k-space-based retrospective 4D-MRI technique

- Aim 2a: To develop a 2D k-space sorting technique using a T2-weighted MRI sequence
- Aim 2b: To develop a 3D k-space sorting technique using a radial k-space acquisition MRI sequence

Aim 3: To develop diffusion-weighted 4D-MRI (4D-DWI) technique

- Aim 3a: To develop a retrospective 4D-DWI technique based on 2D interleaved slice acquisition ordering
- Aim 3b: To conduct initial evaluation of 4D-DWI for motion management and therapy assessment
1.4 Dissertation chapter overview

The dissertation is organized as following:

Chapter 2 is an introduction of the development of image-based retrospective 4D-MRI techniques. It includes three sub-sections, introducing two projects aims at further improving and developing surrogates, and one project aims at improving tumor to tissue contrast, for image-based retrospective 4D-MRI techniques.

Chapter 3 describes 4D-MRI technique with k-space sorting methods. It includes two subsections, introducing k-space sorting methods applied on 2D MRI sequence and 3D MRI sequence.

Chapter 4 presents the development of 4D-DWI technique. The first sub-section introduces a feasibility study for this technique and the second sub-section discusses the effects of 4D-DWI technique on Apparent Diffusion Coefficient (ADC) Measurement.

Chapter 5 summarizes the projects in the dissertation and discusses the future work plan to improve 4D-MRI techniques.
Chapter 2: Further development of image-based retrospective 4D-MRI technique

2.1 Improvement of the 4D-MRI technique based on body-area surrogate using cine sagittal image acquisition

This study was an investigation of sagittal image acquisition for 4D-MRI with Body Area as respiratory surrogate. It was based on a retrospective 4D-MRI technique which uses body area (BA) as an internal respiratory surrogate. An advantage of an internal surrogate over an external surrogate is the elimination of a breathing monitoring device and invasive procedure. Since the breathing signal is directly extracted from the images, internal surrogates have the potential to reduce cost and improve the accuracy of 4D-MRI reconstruction. In this previous study, image acquisition of 4D-MRI was performed in the axial plane, mimicking the multi-cine MR image acquisition scheme. This technique has been demonstrated in both phantoms and human subjects.

The following study for the BA technique further investigated the robustness of the axial BA surrogate in 31 lung and 7 liver cancer patients. It was found that the axial BA surrogate generally matched well with the Real-time Position Management RPM surrogate (Varian Medical Systems, Inc., Palo Alto, CA). It was discovered, however, that the correlation between the two was significantly better in the abdomen than in the thorax. Furthermore, it was found that the accuracy of respiratory phase calculation and 4D-MRI reconstruction can be affected by space-dependent phase shift ($\delta_{SPS}$), i.e. different axial slice positions reach the respiratory peak at different respiratory phases. This phenomenon and its effect on 4D imaging have not been
comprehensively investigated before. Tarte et al. conducted a study to measure the relative volumetric contributions of abdominal and thoracic breathing, which illustrated the difference of volumes proportions per breathing cycle of thoracic and abdominal between thoracic breathing and abdominal breathing \(^{19}\). In addition, Nehrke et al. also investigated the difference of respiratory motion in abdomen and thorax region, as well as the different anatomical directions with MR navigator echo methods \(^{20}\). The observed space-dependent phase shift could potentially influence the reconstruction of 4D-MRI using the BA method. In this study, we investigated the feasibility of 4D-MRI using sagittal image acquisition in combination with BA surrogate. Compared to axial image acquisition, sagittal image acquisition is expected to be a more accurate and robust way of obtaining breathing signal, primarily because respiratory motion occurs mostly in the superior-inferior (SI) and anterior-posterior (AP) directions. Sagittal image acquisition is expected to be less prone to space-dependent phase shift than the axial image acquisition, as proved by 4D-CT. To demonstrate 4D-MRI with sagittal image acquisition, we have validated this technique in a physical motion phantom, a 4D Digital Extended Cardiac-Torso (XCAT) human phantom \(^{23-25}\), healthy volunteers, and evaluated its performance in cancer patients.

### 2.1.1. Research approach

#### 2.1.1.1. Comparison of Axial BA Surrogate and Sagittal BA Surrogate

Both axial and sagittal BA surrogates are potentially affected by space dependent phase-shift, but in different directions that are perpendicular to the imaging plane, i.e., axial BA is affected by phase-shift in SI direction (labeled as \(\delta_{SIS}^{SI}\)) and sagittal BA is affected by phase-
shift in lateral direction (labeled as $\delta_{SPS}^{LAT}$). One potential advantage of sagittal BA over axial BA is that it is less affected by space-dependent phase shift than, i.e., $\delta_{SPS}^{LAT}$ is less than $\delta_{SPS}^{SI}$. To demonstrate that, ideally real-time 4D scans should be performed so that $\delta_{SPS}^{LAT}$ and $\delta_{SPS}^{SI}$ can be simultaneously determined for a direct comparison. However, it is feasible since there is currently no fast real time 4D imaging technique available. We have thus designed two different studies in a complementary manner to investigate this.

In the first study, we performed a retrospective study using selected, high quality 4D-CT scans of real cancer patients as virtual human phantoms and determine $\delta_{SPS}^{LAT}$ and $\delta_{SPS}^{SI}$ via computer simulations. These 4D-CT images have minimal to no motion artifacts and were chosen based on multiple metrics using published criteria. Cine image acquisition was simulated every 2 cm in both axial and sagittal planes based on the 4D-CT images. Breathing curves were determined for these slice positions using the BA method as described in our previous publication. A total of eleven 4D-CT datasets were studied. Figure 1 shows an example of the normalized 10-phase breathing curves of different slice locations for the axial (a) and sagittal (b) acquisitions. Different colors represent different slice positions. Respiratory phases were calculated separately for each individual breathing curve. The peaks were set to Phase 0% (or Phase 100%). The phases for other data points were calculated via linear interpolation. Phase shift was calculated as the standard deviation of the valley phases of all breathing curves. The resultant $\delta_{SPS}^{LAT}$ and $\delta_{SPS}^{SI}$ were compared using the Wilcoxon Signed Rank test.
Figure 1. 10-phase normalized breathing curves at different slice positions for axial acquisition (a) and sagittal acquisition (b) for a representative patient. Different colors indicate different slice positions. Large variations were observed in axial acquisition, while only minimal variation in sagittal acquisition.

In the second study, we performed a prospective study to acquire cine MR images in axial and sagittal planes during breathing and determine $\delta_{LAT}^{SPS}$ and $\delta_{S}^{ST}$ using these images. Six healthy volunteers and one cancer patient were included in this IRB approved study. All scans were performed in a 3.0 T Clinical MR scanner (TrioTim, Siemens Medical Solution, Germany).
The Physiologic Monitoring Unit (PMU) with bellows wrapped around the abdomen was used to record respiratory signal of the subjects during the scans. From the cine MR images, we determined breathing signals at different locations by tracking the motion of body surface using the BA method at the corresponding locations, as shown Figure 2(a) and 2(b). These breathing signals were used to calculate $\delta_{LAT}^{SPS}$ and $\delta_{ST}^{SPS}$ for comparison. Significance was determined using the Wilcoxon-Mann Whitney test.

![Space dependent phase-shift in lateral direction](image1)

![Space dependent phase-shift in Superior-Inferior direction](image2)

(a)  

(b)

Figure 2. Illustration of respiratory motion tracking at different locations using the cine MR images in the axial plan (a) and sagittal plane (b). Gray stripes indicate the rectangular areas where the BA method was applied to measure the breathing signal.

2.1.1.2. Validation of Sagittal BA as Respiratory Surrogate

To validate sagittal BA as a respiratory surrogate, we compared breathing signals determined using the sagittal BA method with those determined using a region of interest (ROI)
feature-based motion tracking method \(^{42}\). This study was performed on the sagittal cine MR images of 10 human subjects, of which 5 were healthy volunteers imaged at the University of Virginia and 5 were cancer patients imaged at Duke University, both on 1.5 T GE scanners. All subjects signed consent forms prior to the IRB-approved studies. Subjects were imaged continuously in a single sagittal plane (for 5 healthy volunteers) or multiple sagittal planes (for 5 cancer patients) using a steady-state precession sequence (labeled as FIESTA by GE and TrueFISP by Siemens). Imaging parameters were: TR/TE, 3.7 ms/1.21 ms; Matrix, 256x166; FOV, 350x300 mm; flip angle, 52°; slice thickness, 5mm; frame rate: ~3 frames/s. Imaging time per slice was 2 minutes for single slice acquisition and ~10 seconds for multi-slice acquisition for all subjects.

For each subject, breathing signals were determined using the sagittal BA method and the ROI motion tracking method and were compared to each other. ROI motion tracking method tracks the ROI on 2D MR images with an in-house MATLAB program \(^{21}\). In the first frame of the MR image series, the ROI to be tracked was manually contoured, and a vicinity searching box within which the ROI was estimated to move was given. Automatic tracking of the ROI in the following MR images was achieved using the maximal cross correlation technique \(^{22}\). Figure 3 illustrates the workflow of extracting breathing signals from sagittal cine MR images using the BA method, which is similar to the axial BA method as described in our previous publication \(^{13}\). In short, each sagittal MR image was processed by applying an estimated image intensity threshold based on image noise to determine the sagittal body contour. Morphological operations were then performed to exclude extraneous pixels induced by noise in the image. BA was defined as the number of pixels within the body contour (white area in Figure 3b). In practice, the BA was calculated only using the central part of the image (grey area in Figure 3b)
where the respiratory movement is most significant. For each sagittal slice, an individual breathing curve (Figure 3c) was generated by plotting the BA as the function of image acquisition time. For multiple slice acquisitions, the complete breathing curve was obtained by plotting all individual breathing curves sequentially (Figure 3(d)).

![Workflow of extracting breathing signals from sagittal MR images using the BA surrogate.](image)

Figure 3. Workflow of extracting breathing signals from sagittal MR images using the BA surrogate. (a) sagittal cine MR images at one slice position; (b) calculation of BA (white area) from sagittal cine MR images. In practice, only the middle section (grey area) was used for BA calculation; (c) the BA-derived breathing curve for a single breathing cycle; (d) the BA-derived breathing curve for multiple breathing cycles in case of multiple slice acquisitions.

To extract the breathing signal using the ROI motion tracking method, an ROI, such as tumor, diaphragm, or pulmonary vessels, was contoured manually in the first frame of the MR image series and then the ROI was tracked automatically in the following frames by searching
the vicinity of the structure and matching with a maximum cross correlation technique. For multiple slice acquisition, the ROI tracking was performed at each slice position, requiring manual contouring of the ROI in the first frame of MR images of each slice position. All breathing curves were normalized prior to the calculation of respiratory phases, using the same method as described in our previous work \(^1\). To validate the sagittal BA as a respiratory surrogate, we compared the breathing curves determined from the two methods using a measure of peak time difference \((\Delta_T^{peak})_i\), which is defined as:

\[
(\Delta_T^{peak})_i = \frac{|(T_{BA}^{peak})_i - (T_{ROI}^{peak})_i|}{period_i}
\]  \[1\]

Where \((\Delta_T^{peak})_i\) is the peak time difference between BA method and ROI tracking method for the \(i^{th}\) breathing curve; \((T_{BA}^{peak})_i\) is the time the \(i^{th}\) breathing curve reaches its peak using BA method; \((T_{ROI}^{peak})_i\) is the time the \(i^{th}\) breathing curve reaches its peak using ROI tracking method; \(period_i\) is the period for the \(i^{th}\) breathing curve.

To quantify the difference between the two methods over several breathing curves, the mean and standard deviation of \(\Delta_T^{peak}\) for several breathing curves measured over a period of time could be calculated:

\[
\overline{\Delta_T^{peak}} = \frac{1}{N} \sum_{i=1}^{N} (\Delta_T^{peak})_i
\]  \[2\]
\[\delta(\Delta_T^{\text{peak}}) = \sqrt{\frac{1}{N} \sum_{i=1}^{N} ((\Delta_T^{\text{peak}})_i - \overline{\Delta_T^{\text{peak}}})^2}\]

Where \(N\) is the total number of respiratory curves, \(\overline{\Delta_T^{\text{peak}}}\) is the mean peak time difference for an individual subject, and \(\delta(\Delta_T^{\text{peak}})\) is the standard deviation of the peak time difference for an individual subject.

### 2.1.1.3. Motion Phantom Study

The 4D-MRI technique with sagittal image acquisition was tested on an in-house constructed MRI-compatible motion phantom\(^{18}\), consisting of a MRI-compatible motion stage and a motion motor (BrainLAB Inc., Feldkirchen, Germany). The motion stage consists of a supporting platform (2 cm solid water slab), an inverse-T shaped motion stage made from styrofoam, a cylindrical gel (radius=2.3 cm, height=3.2 cm), and a 5 mm-thick bolus piece on a plastic flat board. The motion stage was driven by a motor on one end via a surgical low-elastic thread and attached to the other end via a rubber band. The motor was set to move in a sinusoidal wave (peak-to-peak amplitude=2.0 cm, period=5 s), driving the motion stage with cylindrical gel (simulating tumor) to move in the same pattern along the SI direction. Consequently, the bolus piece rotated along the fixed axis, simulating the body surface motion. The triangle area under the bolus was the area under “pseudo chest wall” mimicked the sagittal BA of motion phantom. A photo and structure illustration can be found in reference 13. In our study, the actual motion of the phantom is measured by tracking the motion of the cylindrically shaped gel in the multiple slice cine MR images in the coronal plane.
4D-MRI of the phantom was acquired on a clinical 1.5 T scanner (Signa, GE Healthcare, Milwaukee, WI) using a FIESTA sequence and a six channel phased array coil. Multiple slice sagittal cines were acquired. There is no gap in time between image acquisitions at consecutive slices. The breathing signal extracted from MR images is continuous. The MR sequence used does have a steady state process: the first several images show higher signals than the rest images. This phenomenon has been considered in our technique by removing the first several images from 4D-MRI reconstruction. They are still used when extracting breathing signals, so this will not influence the continuity of the breathing signal. Imaging parameters were: repetition time (TR)/echo time (TE): 3.2 ms/1.0 ms; field of view (FOV): 300x300 mm; flip angle: 50°; slice thickness: 5 mm; matrix: 192x128. Frame rate was approximately 3 frames per second. All images were acquired in the sagittal plane. Using cine mode, each slice was imaged for 6 seconds. The MR images were interpolated to 256x256 before further analysis. BA of the phantom was defined as the area under the bolus piece \(^{17}\) in the sagittal MR images.

Breathing signals were extracted from the sagittal images using the BA surrogate. Respiratory phases were calculated accordingly. 10-phase 4D-MRI images were then reconstructed based on phase-binning. Gel motion extracted from the reconstructed 4D-MRI was compared to that from the coronal multiple slice cine MR.

### 2.1.1.4. Digital Phantom Study

The 4D-MRI technique with sagittal image acquisition was also tested on the 4D-XCAT digital human phantom. The respiratory motion of the 4D-XCAT phantom was modeled using a regular breathing profile. The 4D-XCAT phantom was generated only for the abdomen region...
using the following parameters: in-plane resolution: 256x256; voxel size: 2.5 mm; maximum
diaphragm motion: 2.0 cm; maximum anterior body motion: 1.0 cm; breathing period: 5 s;
frames per breathing cycle: 21. 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. A spherical tumor of 3 cm in diameter was
inserted into the liver.

Virtual experiments of 4D-MRI using the sagittal BA surrogate were carried out on the
4D-XCAT phantom according to the following steps: 1) mimic the image acquisition of 4D-MRI
by continuously extracting images of the same sagittal slice from the 4D-XCAT phantom for
more than one breathing cycle; 2) repeat step 1 for all sagittal slice positions; 3) calculate BA of
each sagittal slice and determine the breathing curve for each slice position ; 4) calculate
respiratory phases for each sagittal slice; and 5) retrospectively sort the sagittal slices based on
their respiratory phases to generate the simulated '4D-MRI'. In order to evaluate the accuracy of
the simulated '4D-MRI', we also generated original 4D-XCAT images using the same respiratory
motion profile as a reference for comparison. Motion trajectories of the tumor were determined
from the simulated '4D-MRI', and compared to those measured from the original 4D XCAT
images.

2.1.1.5. Patient Study

Six patients (4 female, 2 male, mean age 62.0) with cancer(s) located in the liver were
prospectively enrolled in an IRB-approved study. For each patient, multiple slice sagittal MR
images were acquired continuously throughout the breathing cycle for 4D-MRI reconstruction.
Single-slice cine MR was also acquired in the axial, coronal, and sagittal planes across the center of the tumor for 30 seconds. All images were acquired in a 1.5 T GE clinical scanner using the FIESTA sequence, with a frame rate of about 3 frames per second. The subjects were positioned head-first-supine with arms down, and no immobilization device was used. They were instructed to breathe normally during the scans. Each sagittal slice was imaged for approximately 8 seconds. Imaging parameters were summarized in Table 2. Breathing signals were firstly generated by tracking the changes of BA in the sagittal plane, followed by manual inspection and correction for erroneous peak detections. Respiratory phases were calculated and 4D-MRI were reconstructed as described in previous sections. Tumor motion trajectories in the SI, AP, and medial-lateral (ML) directions were determined from 4D-MRI and compared to those from single-slice cine MR images, which served as references. Absolute amplitude difference between 4D-MRI and cine MRI for each respiratory phase bin has been calculated, labeled as absolute error. Furthermore, since each patient has different maximum respiratory motion amplitude for each individual cycle, the absolute error might not adequate to indicate curve differences. The relative amplitude difference, which is defined as the absolute amplitude differences divide by the total absolute amplitude of each individual respiratory cycle were also calculated, labeled as relative error (%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR</td>
<td>2.7 ms</td>
</tr>
<tr>
<td>TE</td>
<td>1.0 ms</td>
</tr>
<tr>
<td>FOV</td>
<td>480×480 mm</td>
</tr>
<tr>
<td>flip angle</td>
<td>50°</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>256×256</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>977 Hz/pixel</td>
</tr>
</tbody>
</table>

Abbreviations: TR: Repetition Time; TE: Echo Time; FOV: Field of View.
2.1.2. Results

2.1.2.1. Comparison of Axial BA Surrogate and Sagittal BA Surrogate

One representative result of the first study is shown in Figure 1. The breathing curves for the axial acquisition have larger valley phase variation than those of the sagittal acquisitions: the valley phases were located among phase 50%, 60%, and 70%, for the axial acquisition, while they were all located in phase 60% for the sagittal acquisition. For example, for the case as shown in Figure 1, $\delta_{SPS}^{SI}$ and $\delta_{SPS}^{LAT}$ was 6.2% and 0%, respectively. Averaging over 11 patients, $\delta_{SPS}^{SI}$ was found to be significantly (p-value: 0.012) greater than $\delta_{SPS}^{LAT}$: the mean (±standard deviation (SD)) $\delta_{SPS}^{SI}$ was 19 (±12) % and 11.5 (±8.2) % for $\delta_{SPS}^{LAT}$ (The median of $\delta_{SPS}^{SI}$ was 16.9 % and 7.8 for $\delta_{SPS}^{LAT}$). Table 3 summarizes the results for all patients.

Table 3. Validation of space-dependent phase shift: Summary of $\delta_{SPS}^{SI}$ and $\delta_{SPS}^{LAT}$ measurements on 4D-CT for 11 cancer patients, along with sign test results.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>$\delta_{SPS}^{SI}$</th>
<th>$\delta_{SPS}^{LAT}$</th>
<th>$\delta_{SPS}^{SI} &gt; \delta_{SPS}^{LAT}$</th>
<th>Total number of axial slices</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.3</td>
<td>25.6</td>
<td>YES</td>
<td>76</td>
</tr>
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<td>20.5</td>
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<td>11</td>
<td>5.94</td>
<td>2.89</td>
<td>YES</td>
<td>120</td>
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</table>

Mean(±SD)[Median] 19 (±12) [16.9] 11.5 (±8.2) [7.8] Sign Test: p=0.012 100 (±22)

Figure 4 shows an example of normalized breathing signals at different locations from the same breathing cycle extracted from the cine MR images. It can be clearly seen that the
breathing signals had greater variation in respiratory phase in the SI direction than in the lateral direction. In both cases the PMU respiratory signal deviated from the BA-derived breathing signals, presumably due to the differences between external surrogate motion and internal anatomical motion \(^{26}\). However, it should be noted that the calculation of phase-shift is independent of the PMU breathing signal. On average of all subjects, the mean \(\delta_{\text{SI}}\) and \(\delta_{\text{LAT}}\) are 4.66% and 2.66% (p-value < 0.0001), [the median of \(\delta_{\text{SI}}\) and \(\delta_{\text{LAT}}\) are 11.0% and 9.8% (p-value: 0.008)] respectively.

Figure 4. Representative respiratory cycles illustrate the space dependent phase-shift in SI direction (a) and lateral direction (b). Color curves shows the body surface motion extracted from MR cine and black curves with dots shows the respiratory signal recorded by PMU.
2.1.2.2. Validation of Sagittal BA as Respiratory Surrogate

Figure 5 shows an example of a good match in normalized breathing signals between the sagittal BA method and the ROI tracking method for a single slice acquisition. Averaging over 5 patients, the mean (± standard deviation) of $\Delta T^{\text{peak}}$ for single slice acquisition was 0.06 (±0.02). Figure 6 shows an example of the comparison in normalized breathing signals between the sagittal BA method and the ROI tracking method for a multiple slice acquisition. Despite difference in the amplitude, the respiratory peaks generally matched well ($\Delta T^{\text{peak}}$ is 0.07 for this patient). Averaging over 5 patients, the mean (±SD) of $\Delta T^{\text{peak}}$ for single slice acquisition was 0.06 (±0.01). Table 4 summarizes the results for all comparisons.

Figure 5. Comparison of breathing signals and respiratory phases between the BA method and the ROI motion tracking method for a single-slice acquisition. Respiratory amplitudes have been normalized.
Figure 6. Comparison in normalized breathing signals between the sagittal BA method (blue) and the ROI tracking method (red) for a multiple slice acquisition. In this example, the imaging time per slice position is slightly more than 2 breathing cycles.

Table 4. Summary of measurements of $\Delta_T^{\text{peak}}$ and $\delta(\Delta_T^{\text{peak}})$ for each patient.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Single slice patients</th>
<th>Multiple slices patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta_T^{\text{peak}}$</td>
<td>$\delta(\Delta_T^{\text{peak}})$</td>
</tr>
<tr>
<td>1</td>
<td>0.059</td>
<td>0.049</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>0.050</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>5</td>
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<td>0.051</td>
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<tr>
<td>Mean</td>
<td>0.061</td>
<td>/</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(±0.022)</td>
<td>/</td>
</tr>
</tbody>
</table>

2.1.2.3. Motion Phantom Study

Figure 7 shows the relative location of the gel target at 10 different phases in all three planes. Sagittal images are the originally acquired images, while axial and coronal images are the reconstructed images of the 4D-MRI. Clear sinusoidal motion is observed in all three planes with minimal image artifacts on the reconstructed images. Interpolation-induced blurring exists on the axial and coronal planes, without substantially degrading the overall image quality. The target motion measured from 4D-MRI is consistent with the input signal, as demonstrated in Figure 8. The mean (±SD) absolute difference in target motion amplitude between the two is 0.70 (± 0.64) mm.
Figure 7. 10-phase 4D-MRI images of a cylindrical gel phantom in (a) axial, (b) coronal, and (c) sagittal planes. Images were acquired in sagittal planes (thus it has high resolution).

Figure 8. Comparison of motion trajectories in SI direction of the imaging object in the phantom study between 4D-MRI and coronal cine MR.

2.1.2.4. Digital Phantom Study

Figure 9 shows the respiratory signals and phases of the 4D-XCAT phantom that are determined using sagittal BA surrogate. Simulated ‘4D-MRI’ of the XCAT phantom matched well
with the original 4D-XCAT phantom, as illustrated in Figure 10. No apparent artifacts were observed. Figure 11 shows that the motion trajectory of the hypothesized tumor matched well with the input motion profile: the mean (±SD) absolute difference in motion amplitude is 1.3 (±0.7) mm in the SI direction and 0.4 (±0.3) mm in the AP direction.

Figure 9. (a) Breathing signals and respiratory phases determined using the sagittal BA method in the digital phantom study. (b) Axial view of the XCAT phantom with a pseudo liver tumor. Organs’ intensities of the XCAT phantom were assigned to mimic T2-weighted MRI. Vertical dash lines indicate the slice positions at which the sagittal cine images were acquired.
Figure 10. Comparison between (a) the original 10-phase 4D-XCAT phantom images and (b) the simulated 10-phase ‘4D-MRI’ images of the 4D-XCAT phantom in axial view; comparison between (c) the original 10-phase 4D-XCAT phantom images and (d) the simulated 10-phase ‘4D-MRI’ images of the 4D-XCAT phantom in coronal view; Dashed lines were added for better visualization of motion. Minimal sorting artifacts were observed in certain phases of the simulated ‘4D-MRI’ images.

Figure 11. Compare breathing curve in SI and AP direction between reconstructed 4D-MRI and original XCAT 3D images.

2.1.2.5. Patient Study

Breathing signals of the six cancer patients were successfully extracted from the sagittal MR images using the BA method. Figure 12 shows an example of the breathing curves of a representative patient (only breathing curves of the right side of the body are shown). 4D-MRI images successfully revealed respiratory motion of all 6 patients. Figure 13 shows the 10-phase 4D-MRI images in the axial and coronal views of a representative patient. Reconstructed
coronal 4D-MRI images are largely consistent with coronal cine MR images, as illustrated in Figure 14 for the same subject. Furthermore, tumor motion trajectories determined from 4D-MRI matched well with those from cine MR, as summarized in Table 5. Averaging over 6 patients, the mean (±SD) absolute differences in tumor motion amplitude between 4D-MRI and cine MR were 1.5 (±1.6) mm, 2.1 (±1.9) mm, and 1.1 (±1.0) mm in the SI, ML, and AP direction, respectively. Figure 15 shows an example of the comparisons of the tumor motion trajectories.

Figure 12. Breathing signals (for only the right side of the body) extracted from sagittal MR images using the BA surrogate. Dash lines indicate the imaged sagittal planes.

Figure 13. 10-phase axial and coronal 4D-MRI of a representative patient.
Figure 14. 10-phase coronal images of the liver in cine MR images (a) and 4D-MRI images (b) of a representative patient.

Table 5. Tumor motion trajectories comparison in patient study, 4D reconstructed images with reference from single-slice cine MR. Measurements of tumor CNR comparing CT and MRI fast sequence FIESTA.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age</th>
<th>Gender</th>
<th>Cancer site</th>
<th>Mean absolute error (mm)</th>
<th>Amplitude from cine (mm)</th>
<th>Relative error (%)</th>
<th>CNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Liver Mets</td>
<td>4.7</td>
<td>2.4</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>F</td>
<td>HCC</td>
<td>0.25</td>
<td>0.12</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
<td>Liver Mets</td>
<td>1.0</td>
<td>2.4</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>HCC</td>
<td>1.5</td>
<td>0.63</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>HCC</td>
<td>0.42</td>
<td>0.38</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>F</td>
<td>HCC</td>
<td>1.2</td>
<td>0.87</td>
<td>3.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Mean (±SD) 65.0 (±9.7) 1.5 (±1.6) 2.1 (±1.1) / (±1.0) 1.7 (±2.0) / / 14 (±9.1) 21 (±16) 50 (±35) 2.1 (±1.5) 15 (±21)

Abbreviations: F: female; M: male; SD: standard deviation; SI: superior-inferior; AP: anterior-posterior; ML: medial-lateral; CNR: contrast-to-noise ratio; CT: computed tomography; FIESTA: fast imaging employing steady state acquisition; HCC: Hepatocellular carcinoma; Liver Mets: liver metastasis.
Figure 15. Comparison of tumor motion trajectories between 4D-MRI and cine MR.

It is feasible to extract breathing signals from sagittal cine MRI images using BA as the respiratory surrogate. 4D-MRI using sagittal image acquisition in combination with the BA surrogate demonstrated good accuracy in respiratory motion measurement in our preliminary study. Further investigation is warranted to assess the robustness of the 4D-MRI technique with the sagittal BA surrogate.

2.2 Investigation of the sagittal-coronal-diaphragm point of intersection (SCD-Poi) as respiratory surrogate for retrospective 4D-MRI

In this study, we developed a retrospective 4D-MRI with image-based surrogate: a sagittal-coronal-diaphragm point of intersection (SCD-Poi) motion tracking method. We investigated the feasibility of 4D-MRI for respiratory motion imaging in abdominal region with an image-based internal respiratory surrogate tracking diaphragm motion in SI direction on sagittal-coronal intersecting lines. Compared to BA method, this method is expected to be a more accurate and robust way of obtaining breathing signal, primarily because it extracts respiratory motion in the dominant motion direction of diaphragm, the SI direction. This reduces or
eliminates the possibility of missing respiratory motion vibrations on 4D-MRI. To demonstrate the 4D-MRI technique with this novel surrogate, 4D digital human phantom XCAT simulation and a human subject study have been conducted.

2.2.1 Research approach

2.2.1.1. 4D-MRI Technique

Image acquisition of the 4D-MRI technique with SCD-Pol surrogate is a two-step process. First, a fast steady state acquisition imaging technique (labeled as FIESTA by GE and TrueFISP by Siemens) was employed to acquire single-slice sagittal cine images at a slice location near the dome of diaphragm. This MR sequence was chosen because it provides good tumor contrast and high temporal resolution (up to 6–8 frames/s). This sequence has been widely used for tumor motion imaging\textsuperscript{28-32}. This acquisition was performed for 1-2 min and was used as a pre-estimation of the respiratory motion pattern for each subject. MRI parameters were optimized to balance spatial resolution (about 1.5 mm in-plane), temporal resolution (about 4 frames/s) and SNR. Second, the same MR sequence was employed to acquire multi-slice coronal cine images covering most of the lung and the entire liver region. The images acquisition time for each cine slice location was set to be 20-30 seconds to assure it was longer than one respiratory cycle. The coronal images were retrospectively sorted to reconstruct 4D-MRI. All the coronal image planes intersected with the sagittal image plane. The intersecting lines of the sagittal image plane and each coronal image plane were labeled as sagittal-coronal intersecting lines (SCL) in our study. SCL can be observed on both the sagittal cine and the coronal cines. The point of intersection of each SCL with the diaphragm was tracked as a
surrogate of respiratory motion, as shown in Figure 16. The point of intersection of diaphragm with each SCL is labelled as sagittal-coronal-diaphragm point of intersection (SCD-PoI).

Figure 16. Workflow of 4D-MRI using SCD-PoI as the respiratory surrogate.

Each the coronal slice location has an associated SCL on the sagittal single-slice cine. Therefore, SCD-PoI motion can be extracted from the sagittal cine images, as shown in Fig.1 in the upper row with the red curve. Each red dot on the curve represents one 2D image of the
sagittal cine. Average breathing curve can be calculated from it as a pre-estimation of respiratory motion pattern for the subject. This average respiratory curve was divided into several respiratory phases, and the motion amplitude range of each phase bin were determined. Meanwhile, since the SCL can also be observed on the coronal cine at the corresponding slice location, the same SCD-PoI can also be tracked on the coronal cine, as shown with the black curve in Fig.1. Each black dot on the curve represents one 2D image from the coronal cine at one example slice location. Coronal cines were acquired at multiple slice locations for 4D reconstruction. With the diaphragm motion amplitude information determined from this curve, amplitude sorting was conducted for the coronal cine images. This process was repeated for each coronal cine slice location to generate 4D-MRI. Amplitude window of each bin was determined from the sagittal cine estimation. All image processing, motion detection and 4D reconstruction were performed automatically using an in-house program implemented in Matlab (The MathWorks Inc., Natick, MA).

2.2.1.2. Digital Phantom Study

The 4D-MRI technique with SCD-PoI surrogate was tested on the 4D-XCAT digital human phantom developed by Segars et al.\textsuperscript{23-25}. The respiratory motion of the XCAT phantom was controlled by an input regular breathing profile. The XCAT phantom was set in the activity mode in order to produce MRI-like images for the chest and abdomen region. The parameters used included: in-plane image matrix: 256x100; voxel size: 2.5×3 mm; slice thickness: 5 mm; maximum diaphragm motion: 30 mm; maximum anterior body motion: 10mm; breathing period:
5 s; frames rate 5 frames/s. A spherical hypothesized tumor of 30 mm in diameter was inserted into the phantom’s liver. The tumor motion was the same as its surrounding liver tissue.

Virtual experiments to implement the novel 4D-MRI technique were carried out on the 4D-XCAT phantom in the following steps: 1) a regular respiratory motion profile was input to XCAT to control the motion of the phantom. We took a volumetric MRI snap-shot of the phantom at the same imaging frame rate of the actual MR sequence (e.g., 5 frames/s). The phantom continued moving for 680 s. This resulted in a large number of volumetric image datasets, each corresponding to a different breathing state. These datasets would be the digital moving phantom that we simulate image acquisition process on; 2) mimic the image acquisition of single-slice sagittal cine and multi-slice coronal cine by extracting 2D MRI images from the volumetric MRI snap-shots generated in step 1. Single-slice sagittal cine was acquired for 80 s, and multi-slice coronal cines were acquired for 20s×30slices; 3) track the diaphragm motion at SCD-Pol on sagittal cine and coronal cines. In order to validate the SCD-Pol as a respiratory surrogate, the breathing signal extracted using SCD-Pol was compared with the input breathing profile; 4) pre-estimate the respiratory motion pattern with SCD-Pol signal extracted from single-slice sagittal cine. The respiratory motion range (i.e. amplitude window) of each phase bin on the average breathing curve was determined; and 5) extract SCD-Pol signal from multi-slice coronal cine images. We retrospectively sorted the coronal images based on the comparison of the pre-estimated amplitude motion range of phase bin and the SCD-Pol respiratory motion amplitude of each coronal cine images, to generate the ‘4D-MRI’.

In order to evaluate the accuracy of respiratory motion information demonstrated on the simulated ‘4D-MRI’, tumor trajectories on the reconstructed 4D-MRI were measured and compared with average breathing curve calculated from the input respiratory profile. Mean
absolute amplitude difference (D) and cross-correlation coefficient (CC) in SI direction were measured.

2.2.1.3. Human Subject Study

The feasibility of the 4D-MRI technique was tested on six healthy volunteers (4 males and 2 females, mean age 30) and two cancer patients (1 male and 1 female, mean age 65). All healthy volunteers and patients were prospectively enrolled in an IRB-approved study. The MR images for the healthy volunteers were acquired on a Siemens 3T system using TrueFISP sequence for single-slice sagittal and multi-slice coronal cines. Imaging parameters were: TR/TE, 2-4 ms/1-2 ms; FOV, ~400x400mm; flip angle, ~35°; pixel size 1-2 mm; slice thickness, 5 mm; matrix, 192x162; bandwidth, 1371 Hz/pixel. Imaging frame rate was 4-5 frames/s. The sagittal cine was imaged for 66 s. The coronal cines were imaged for 12.6s×30slices. The cancer patients' MR images were acquired on a GE 1.5 T system using a FIESTA sequence. Imaging parameters were: TR/TE, 2-4 ms/1 ms; FOV, ~400x400 mm; flip angle, 50°; pixel size 1-2 mm; slice thickness, 5 mm; matrix, 256x256; bandwidth, 976.562 Hz/pixel. Imaging frame rate was 2-4 frames/s. The sagittal cine was imaged for 63 s. The coronal cines were imaged for 10.1s×30slices. All subjects were positioned head-first-supine with arms down, with no immobilization device. They were instructed to breathe normally during the scans.

4D-MRI was reconstructed with SCD-Pol surrogate using the following steps: 1) single-slice sagittal cine and multi-slice coronal cine using TrueFISP sequence with the above parameters; Single-slice sagittal cine was acquired for 80 s, and multi-slice coronal cines were acquired for 20s×30slices; 2) diaphragm motion at SCD-Pol on sagittal cine and coronal cines
was tracked to generate breathing signal; 3) respiratory motion pattern was pre-estimated with the extracted breathing signal from single-slice sagittal cine. The respiratory motion range, i.e., amplitude window, of each phase bin on the average breathing curve was determined; and 4) the coronal images were retrospectively sorted based on the SCD-Pol breathing motion signal extracted from them and the respiratory motion pre-estimation obtained in step 3) to generate 4D-MRI.

To evaluate the accuracy of the respiratory motion of 4D-MRI, single-slice sagittal cine MR images were acquired across the center of the tumor (in patients) or a hepatic vessel near the liver center (in healthy subjects), providing ground-truth of tumor motion for comparison. Motion trajectories of the region of interest (ROI) in the SI direction were determined from 4D-MRI. The trajectories were compared with the average breathing curve calculated from ROI trajectories tracked on single-slice cine MR images. D and CC were calculated to quantitatively evaluate the 4D-MRI image quality.

2.2.2 Results

2.2.2.1. Validation Study

Figure 17(a) shows the respiratory signals of the 4D-XCAT phantom determined from sagittal cine using SCD-Pol and its comparison with the input breathing profile. The mean absolute amplitude difference is 1.18 mm. Also, the respiratory signal from one slice of coronal cine is shown in Figure 17(b) with the comparison with the input profile. The mean absolute amplitude difference is 1.73 mm.
Figure 17. Breathing signals (black curve with triangles) extracted using SCD-Pol from single-slice sagittal cine (a) and one slice of multi-slice coronal cine (b). Both of the signals matched well with the input breathing profile (gray curve with circles).

2.2.2.2. Digital Phantom Study

Simulated ‘4D-MRI’ of the XCAT phantom demonstrates highly accurate respiratory motion, as shown in Figure 18(a). No apparent artifacts were observed. Figure 18(b) shows that the tumor motion trajectory in the SI direction demonstrated on 4D-MRI matches well with the average breathing curve calculated from the input motion profile: D is 1.13 mm and CC is 0.98.
2.2.2.3. Human Subject Study

Figure 19 shows an example of the breathing curves of a representative human subject extracted from MR cine using SCD-Poi as a surrogate. Figure 20(a) shows the 4D-MRI of a representative healthy volunteer. Figure 21(a) shows the reconstructed 4D-MRI of one representative cancer patient. A benign cyst in the liver is pointed out by the white arrow. Minimal artifacts are observed in the 4D-MRI of human participants, with adequate motion information demonstrating the organs and tumors' respiratory motion. Furthermore, the ROI or
tumor motion trajectories determined from 4D-MRI match well with those of the reference cine MRI, as illustrated in Fig. 20(b) for the representative healthy volunteers and Fig. 21(b) for the representative cancer patient. D and CC were calculated for all human subjects and they were summarized in Table 6. On average of all 6 healthy volunteers and 2 patients, the mean (±Standard Deviation) D is 1.08 (±1.03) mm and CC is 0.96 (±0.05) in the SI direction.

Figure 19. Breathing signals extracted from a representative human subject using SCD-Pol as a surrogate.
Figure 20. 6-phase 4D-MRI images of a representative healthy volunteer with relatively large respiratory motion (a). Comparison of ROI motion trajectories determined from 4D-MRI with those from reference cine MR (b).
Figure 21. 6-phase 4D-MRI images of a representative cancer patient. A benign cyst in liver is pointed out by the white arrow (a). Comparison of tumor motion trajectories determined from 4D-MRI with those from reference cine MR (b).

Table 6. D and CC measurement in SI direction summary for all human subjects, in plane pixel size is 1.88 mm for patients; 2.08 mm for healthy volunteers. Slice thickness are 5 mm for all human subjects.

<table>
<thead>
<tr>
<th>Human subject #</th>
<th>D (mm)</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteer 1</td>
<td>0.94</td>
<td>0.98</td>
</tr>
<tr>
<td>Healthy volunteer 2</td>
<td>1.85</td>
<td>0.94</td>
</tr>
<tr>
<td>Healthy volunteer 3</td>
<td>0.92</td>
<td>0.98</td>
</tr>
<tr>
<td>Healthy volunteer 4</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Healthy volunteer 5</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Healthy volunteer 6</td>
<td>0.58</td>
<td>0.89</td>
</tr>
<tr>
<td>Patient 1</td>
<td>3.11</td>
<td>0.89</td>
</tr>
</tbody>
</table>

41
Patient 2  1.25  0.99  
Mean (±SD)  1.08(±1.03)  0.96(±0.05)  

D: Mean absolute amplitude difference; CC: cross-correlation coefficient.

2.3 Development and evaluation of a T2-weighted retrospective 4D-MRI technique using sequential image acquisition

T2-weighted MRI sequence Fast Recovery Fast Spin Echo (FRFSE) is the clinical standard MR sequence for liver cancer diagnosis \(^{33-35}\), often presenting higher tumor contrast than T2/T1-weighted MRI. It is therefore highly desirable to develop 4D-MRI technique with T2-weighted contrast. However, T2-weighted MRI usually requires long repetition time and therefore results in low temporal resolution, making them suboptimal choices for 4D imaging. In compensation for the low temporal resolution of FRFSE MRI sequence, we considered using a Half-Fourier Acquisition Single-Shot Turbo Spin-Echo (HASTE/SSFSE) MR sequence, which is a T2-weighted, high speed sequence with partial Fourier technique, for 4D-MRI image acquisition. The frame rate of HASTE/SSFSE sequence is approximately 2-3 frames/s, sufficient for 4D-MRI image acquisition. Recently, Hu et al have proposed a prospective 4D-MRI technique based on the HASTE/SSFSE sequence \(^9\). In their study, a respiratory triggering system was developed to prospectively guide 4D-MRI acquisition. The reconstructed 4D-MRI achieved great soft-tissue contrast. However, the technique required hardware adjustment for MR scanner. For example, triggering system was adjusted to acquire image for multiple respiratory states, rather than just one. Also, adjustments were made to display markers on the console computer during the time when k-space was sampled. The markers were used to indicate the active image acquisition period on the individual’s respiratory waveform.
Current retrospective 4D-CT \(^{5-8}\) and 4D-MRI \(^{13}\) techniques typically acquire images in cine or slow-pitch helical mode. With these techniques, 2D images are continuously acquired at the same slice position (or nearly the same slice position in the helical mode) for a period of time. The process is then repeated at multiple slice positions to cover the volume of interest. To satisfy data completeness condition \(^{36}\), i.e., when images of all sorting bins and all slice positions have been acquired, imaging time per slice position is set to be longer than patient’s breathing period. This sorting process, however, cannot be applied to retrospective T2-weighted 4D-MRI using HASTE/SSFSE sequence. HASTE/SSFSE sequence acquires image for volume of interest in sequential mode, which includes ascending, descending, and interleaved sub-modes. This scanning for volume of interest was repeated a pre-set number of times, which was pre-estimated via computer simulations. The acquisition scheme is shown in Figure 22. With this different image acquisition scheme, our current research aim is to develop a phase sorting technique for sequential acquisition mode to utilize HASTE/SSFSE MRI sequence to reconstruct T2-weighted 4D-MRI.

There are mainly two problems in developing the technique. Firstly, due to the relatively stochastic respiratory phase for each acquired 2D image, the 4D-MRI image acquisition time is not obviously and directly predictable. The 4D-MRI data sufficient condition can be affected by multiple factors, including the number of repetitions (\(N_R\)), the number of slices (\(N_S\)), the number of sorting bins (\(N_B\)), the initial respiratory phase at the start of image acquisition (\(P_0\)), the patients’ breathing period (\(B_P\)) and the breathing variation (standard deviation of breathing period, \(B_V\)). Secondly, multiple images might be sorted to one phase bin at a slice location. The image redundancy requires an effective utilization of these images to generate 4D-MRI.
In this study, we present our approaches to resolve these challenges in developing the retrospective T2-weighted 4D-MRI. In particular, we have developed computer simulation programs to study the relationships between data completeness and associated factors. We have also developed a result-driven sorting strategy to effectively utilize redundant images for each phase bin. Our T2-weighted MRI technique has been validated and tested on the digital human phantom XCAT and human subjects.
Figure 22. Image acquisition mode comparison for cine mode (a) and T2-weighted HASTE/SSFSE MR sequential mode, which includes ascending, interleaved and descending sub-modes (b). In figure (a), the top row shows the respiratory signal recorded and the bottom row shows the image acquisition locations. In figure (b), the top row demonstrates the respiratory signal recorded, and the second, third and bottom rows demonstrate image
acquisition locations for the ascending mode, interleaved mode and descending mode, respectively.

With the sequential-mode T2-weighted 4D-MRI technique for imaging respiratory motion being developed. We also compared the sequential image acquisition mode with the widely used cine image acquisition mode for 4D imaging. We investigated which 4D-MRI image acquisition mode provides more accurate measurement of organ motion during respiration.

2.3.1 Research approach

2.3.1.1. Result-Driven Retrospective Sorting

The 4D-MRI sorting technique is applied on a fast 2D MR sequence HASTE/SSFSE in the axial plane with free breathing. The sequence has high temporal resolutions (~2 frames/s) and a good tumor visibility. The acquisition time for each 2D MR image can be synchronized with respiratory signal recorded by the external surrogate, so that the respiratory phase for each image can be calculated from the synchronized respiratory signal. No couch position movements are needed for 4D-MRI. If two peaks are detected before and after the time point of interest, the phase of the peak before will be defined as 0% and the peak after will be defined as 100%. Linear interpolation will be applied to the time points in between to determine the respiratory phase for each time point, as follows:

\[ \varphi = \frac{t - t_{0\%}}{t_{100\%} - t_{0\%}} \times 100\% \text{, if } t_{100\%} \leq t \leq t_{0\%} \]

Where \( \varphi \) is the phase for the time point of \( t \), which is between 2 peaks. \( t_{0\%} \) is the time of the peak immediately before \( t \), and \( t_{100\%} \) is the time of the peak right after \( t \).
In the beginning of the breathing profile, for the time points before the first respiratory peak, $t_{100\%} - t_{0\%}$ of the first incomplete breathing cycle will be estimated by the period of the cycle nearby (the first complete breathing cycle). Linear interpolation will still be applied to calculate $\varphi$ for the time point $t$; similar process will be applied for the last breathing period of the breathing profile. Peak detection can be plotted, checked and revised manually. By synchronizing 2D MR images and the breathing profile, phases can be derived for each image using formula [4].

The retrospective sorting is based on the calculated phases for each image. The sorting process is shown in Figure 23. For illustration purposes, the total number of slices is set to be 8 and the total number of phase bins is set to be 6. Image acquisition and sorting for slice 1 (labeled as “s1” in Figure 22) is illustrated as an example. Acquired images for s1 are assigned to different phase bins according to their respiratory signals. This sorting will be conducted for each slice to generate 4D-MRI dataset.
Figure 23. Illustration of phase sorting process with result-driven strategy. For illustration purposes, the total number of slices is set to be 8 and the total number of respiratory phase bins was set to be 6. Sequential acquisition mode is used to repeatedly (labeled as repetition #) acquire 2D MRI images for volume of interest. Slice location information and respiratory signal are recorded with image acquisition. Red S-number is the slice location index for each 2D MR image and respiratory phase is calculated accordingly. The sorting process is illustrated on slice
1 as an example. 7 images for slice 1 from 7 repetitions come from different respiratory phases. Each of them is assigned to a phase bin. Result-driven strategy is applied to the phase bin with redundant images. The one with minimum amplitude error as compared with average breathing curve will be selected as a component of the 4D dataset.

If redundant images are acquired, i.e., more than one 2D image are binned to one phase bin and result-driven strategy is applied to select the best one to generate 4D-MRI. As shown in Figure 24, this strategy uses the average respiratory curve (gray curve), which is calculated from the entire breathing signal recorded by the external surrogate, as the targeted motion results that we are trying to achieve. The respiratory amplitudes of all the acquired images (black dots) for one bin are compared with the curve. More specifically, average amplitudes for each phase bins (gray dots on the gray curve) are calculated to be compared with the respiratory amplitude of each image (black dots). The images with minimum absolute amplitude error as compared with the average amplitude of its corresponding phase bin will be selected to generate 4D-MRI dataset.

![Graph showing respiratory curve and phase bins](image-url)
Figure 24. Amplitudes of each acquired images (black dots) for each phase bin on the average respiratory curve (gray curve). The images with minimum absolute amplitude error as compared to average amplitude (gray dots on gray curve) of each phase bin will be selected to generate 4D-MRI dataset. Dark gray straight line represents phases for the respiratory curve.

As the number of repeated scan for the volume of interest increases, 4D-MRI dataset will be filled with images from each phase bin and slice location. We quantify dataset completeness ($C_P$, %) for each slice as the relationship between the number of bins with image filled ($N_i$) and the total number of phase bins for this slice ($N_B$):

$$C_P(\%) = \frac{N_i}{N_B} \quad [5]$$

As time increases, the dataset completeness for each slice keeps increasing. Dataset completeness simulation using one representative patient’s breathing profile has been conducted as an example to show how dataset completeness increases with time. As shown in Figure 25 in gray bars, 20 slices as the volume of interest and 10 phase bins are demonstrated as an example. For the entire volume of interest, we extend the definition for data completeness for each slice to a volumetric definition, defining 4D dataset completeness (4D $C_P$, %) as the relationship between the number of bins with image filled for all slices ($N_{i, all}$) and the total number of phase bins for all slices ($N_{B, all}$):

$$4D \ C_P(\%) = \frac{N_{i, all}}{N_{B, all}} \quad [6]$$

A completeness curve can be generated to illustrate the 4D dataset collection progress as time increases, as shown in Figure 25 black curve with $N_R$ labeled.
In case 4D $C_p$ (%) is less than 100%, where there could be missing images for a phase bin, the nearest adjacent phase in the same slice location will be used as a representative of that phase bin.
Dataset completeness for each slice increases with the acquisition time. 20 slices as the volume of interest and 10 phase bins are demonstrated as an example. Dataset completeness ($C_P$, %) for each slice increases with time as illustrated by gray bars and the corresponding 4D dataset completeness ($4D C_P$, %) curves are shown in black curve with $N_R$ labeled.

### 2.3.1.2. Digital Phantom Validation Study

The T2-weighted 4D-MRI technique was tested on the 4D-XCAT human phantom with a regular breathing profile (period: 5 s). XCAT was programed to move with the given diaphragm motion in the SI direction and with the given chest wall motion in the AP direction. The peak-to-peak motion amplitude was set to 3.0 cm and 1.0 cm for the diaphragm and chest wall, respectively. The XCAT images were generated only for the abdominal region using the following parameters: in-plane resolution: 256x256; voxel size: 1.25 mm; slice thickness: 3 mm; frame rate: 2.48 Hz. The XCAT phantom was generated in the activity mode for MRI-like image appearance where the signal intensities of the organs and tissues were assigned using values derived from HASTE/SSFSE MRI images. A hypothesized spherical tumor of 15 mm in diameter was located in the center of the liver.

The simulation of the proposed T2-weighted 4D-MRI technique was carried out on the 4D-XCAT phantom in the following steps: 1) mimicking the image acquisition of HASTE/SSFSE sequence by sequentially (ascending, descending, or interleave) extracting axial 2D XCAT images from the 4D XCAT phantom for a volume of interest; 2) repeating Step 1 for a number of times. The number of repetitions should be large enough to satisfy data completeness condition,
as demonstrated in the previous section. In this phantom study, the total number of repetition was set as 30; 3) calculating the respiratory phase for each extracted 2D XCAT image; and 4) generating the simulated T2-weighted ‘4D-MRI’ by re-binning the 2D XCAT images using the result-driven retrospective sorting method. The total number of phase bins was set as 10 in this phantom study.

The simulated ‘4D-MRI’ using the phase sorting technique was validated by comparing it with the original 4D-XCAT phantom which was generated using the same respiratory motion profiles and imaging parameters. The motion trajectories of the hypothesized tumor were determined from the simulated ‘4D-MRI’ and compared to those measured from the original 4D-XCAT images. The relative amplitude error in motion trajectories were calculated in SI and AP directions.

2.3.1.3. Digital Phantom Studies of Variable Breathing: Data Completeness and Impacting Factors

In order to estimate the image acquisition time needed for retrospective T2-weighted 4D-MRI, and to study the relationships between data completeness and potential affecting factors ($N_R$, $N_S$, $N_B$, $P_0$, $B_P$, and $B_V$), we performed a computer simulation study using simulated irregular respiratory signals and real patients’ respiratory signals. The simulated signals included 2500 irregular breathing profiles whose periods were between 0 to 10 seconds with random breathing variations. Patients’ respiratory signals were the Real-time Position Management (RPM) (Varian Medical Systems, Inc., Palo Alto, CA) breathing signals recorded during the patients’ clinical 4DCT scans. A total of 29 cancer patients’ (13 females and 16
males, 10 abdominal cancers and 19 lung cancers) RPM signals were used in the simulation. We repeated the whole RPM data trace when the total duration was not long enough for the 4D-MRI simulation. The 29 cancer patients were enrolled in an IRB-approved retrospective study. All three image acquisition modes (ascending, interleaved, and descending) were tested in the simulation.

As the total number of 2D MR images acquired increases, the 4D dataset completeness increases, until it reaches 100%. A threshold of completeness should be determined to measure the total scanning time needed to acquire enough 2D images for 4D reconstructions. In our simulation, in order to estimate the threshold, a regular breathing motion profile and 29 patients' breathing motion profiles were used as an input for XCAT to control its motion, with the moving tumor diameter set at 15 mm. Different scans or exam times were simulated by sampling contiguous motion subsets of the simulated XCAT data, setting the total number of slices at 30 and the number of bins at 8 for regular breathing motion profile (6 for patients' breathing motion profiles). With the reconstructed 4D images for different total scanning time, the trajectory of the tumor in SI direction of the tumor in each phase bin can be measured and compared to the original input for XCAT, and relative amplitude error was calculated. Based on the relationship between percentage of completeness and the relative trajectory amplitude error, threshold of the completeness percentage can be determined.

With the threshold set above, completeness curves were calculated for each of the 29 patients' respiratory profiles, and the number of repeated scans when completeness reached the set threshold ($N_{R,\text{threshold}}$) was measured. The total number of bins was set to be 6 and the total number of slices was set to be 30 for phase sorting. Different image acquisition and 4D reconstruction parameters, including the total number of phase bins ($N_B$), the total number of
slices (Ns) of the volume of interest and the starting phase of the scanning ($P_0$) were tested. The relationship between $N_{R,\text{threshold}}$ and the above parameters were investigated.

Furthermore, $N_{R,\text{threshold}}$ could be influenced by the respiratory motion irregularity. The 2500 respiratory profiles were not related to the 29 patients’ breathing profiles. They were generated separately by varying $B_P$ (ranges from 0 to 10s, the interval is 0.2s) and $B_V$ (ranges from 0 to 5s, the interval is 0.1s) to study the relationship between the breathing irregularity and $N_{R,\text{threshold}}$. To generate breathing irregularities in any one of these breathing profiles, random (and thus different) period values were assigned to each breathing cycle of the profile, where the period values were generated based on each breathing profile’s $B_P$ and $B_V$ values.

2.3.1.4. Comparison of Cine and Sequential Image Acquisition Modes

2D cine and sequential image acquisition modes are shown in Figure 26 and Figure 27, respectively. In the top rows, each black dot represents one 2D-MR image acquisition. The bottom row shows the simultaneously recorded respiratory signals. For both acquisition modes, each 2D MRI image is subsequently re-binned according to its respiratory phase or amplitude to generate 4D-MRI.
Figure 26. Illustration of cine image acquisition mode for 4D-MRI. This acquisition mode acquires 2D images continuously at the same slice position for a period of time, and then the process is repeated at multiple slice positions to cover the entire volume of interest (VOI). Each black dot represents one 2D-MR image acquisition. The respiratory signal is simultaneously recorded for 4D-MRI retrospectively sorting purpose.

Figure 27. Illustration of sequential image acquisition mode for 4D-MRI. This image acquisition mode repeatedly acquires 2D MR images sequentially for the volume of interest. Each black dot represents one 2D-MR image acquisition. The respiratory signal is simultaneously recorded for 4D-MRI retrospectively sorting purpose.
To evaluate and compare the performance of the cine-mode and the sequential-mode 4D-MRI techniques, we conducted virtual experiments on the 4D-XCAT digital human phantom by simulating step-by-step the image acquisition and reconstruction of the two 4D-MRI techniques. An in-house developed MATLAB program was built to facilitate the simulation and evaluation. Figure 28 illustrated the overall study design and workflow of the digital phantom simulation study. A subset of the XCAT phantom was generated from the mid-thorax to mid-abdomen region and used in this study. The XCAT phantom was generated in the activity mode for MRI-like image appearance where the signal intensities of the organs and tissues were assigned using values derived from HASTE/SSFSE MRI images. The acquisition mode of that sequence is in sequential mode. Although cine mode 4D-MRI is achieved by using TrueFISP/FIESTA sequences, the same image intensity assignment is used in the cine-mode 4D-MRI XCAT simulation for image quality comparison purpose. The HASTE/SSFSE MRI image intensities were selected for both simulations also because it provided T2-weighted signals, which have a high tumor-to-tissue contrast. Tumor size and respiratory motion pattern were also set to be the same between two modes. In other words, all the basic imaging parameters were set to be the same to compare the image acquisition mode. Only 4D-specific factors was varied to understand how the performances of the 4D-MRI techniques are influenced by respiratory motion variation from the 4D perspective. In particular, the respiratory motion of the XCAT phantom was controlled by a customizable input signal. Maximum diaphragm motion in SI direction was set to be 30 mm; and maximum chest surface motion in AP direction was set to be 10 mm. No motion was input in ML direction. A hypothesized spherical tumor of 40 mm in diameter was inserted at the center of the liver.
To simulate cine-mode or sequential-mode 4D-MRI, a series of volumetric datasets of the 4D-XCAT phantom was first generated in the same imaging frame rate of the actual 2D MR sequence (e.g., 2 frames/s). This resulted in a large number of volumetric XCAT image datasets, each corresponding to a different breathing status. These datasets would be the digital moving phantom that we would simulate image acquisition process on. Secondly, one single slice 2D XCAT image was extracted from each volumetric XCAT image dataset, mimicking the image acquisition as the real MR sequence does. The extraction of the 2D images can be carried out in either cine or sequential mode, following the corresponding scheme as shown in Figure 26 and Figure 27. Thirdly, the extracted 2D images were used to reconstruct 4D-MRI using sorting methods that we have previously developed for both modes.

Simulated imaging parameters in the XCAT phantom study were the following: in-plane resolution: 256x256; voxel size: 2.5 mm; slice thickness: 3 mm; total number of slices: 30; frame rate: 2 Hz; total number of 4D-MRI phase bins: 6. For the cine mode, the scanning time for each slice was 8 seconds, and the total scanning time was 240 s. For the sequential mode, the total scanning time was set to be long enough (300 s) to ensure sufficient sampling of all respiratory phases for 4D-MRI reconstruction.

To quantitatively assess the accuracy of respiratory motion measurement of 4D-MRI, two evaluating metrics were calculated and compared between the cine-mode 4D-MRI and the sequential-mode 4D-MRI. The first metric is the error in tumor motion trajectory (E). The motion trajectory of the hypothesized tumor was first measured from the simulated 4D-MRI images using an in-house developed motion tracking algorithm that was based on maximum cross-correlation, and then compared to an average respiratory curve derived from the input signal.
to determine E. As shown in Figure 29(a), E was calculated as the phase-averaged absolute difference in tumor motion amplitude between the two curves. E was determined for both the cine-mode 4D-MRI and the sequential-mode 4D-MRI, and labeled as $E_{cine}$ and $E_{seq}$, respectively. It should be noted that E evaluates the performance of 4D-MRI only in terms of tumor motion; it does not evaluate the performance of 4D-MRI at non-tumor regions.

To assess the overall performance of 4D-MRI of the entire volume, we introduced a second evaluating metric, the mean difference from the average breathing signal across all slice positions (D). The determination of D includes 3 steps: 1) derive the average breathing cycle from the input breathing signal; 2) generate individual breathing cycle for each slice position during 4D-MRI reconstruction, each selected MR image corresponded to a data point in the input breathing signal, and each data point has an unique set of phase and amplitude. The individual breathing cycle is generated by sorting the selected data points of that slice position based on respiratory phase. Each phase image at a particular slice position has corresponding respiratory amplitude that can be read from the respiratory signal recorded simultaneously with external surrogate. Based on these recorded amplitude information, individual breathing cycle for each slice position can be generated; 3) compare all individual breathing cycles to the average breathing cycle to determine D, as shown in Figure 29(b). D was calculated for both the sequential-mode 4D-MRI and cine-mode 4D-MRI, and was labeled as $D_{seq}$ and $D_{cine}$, respectively.
Figure 28. Flow chart of quantification of 4D-MRI respiratory motion measurement accuracy for both sequential and cine image acquisition mode.
In order to demonstrate the image quality difference between the two 4D-MRI techniques, we designed a particular respiratory motion to control XCAT, and reconstructed the 4D-MRI using the two techniques with different image acquisition modes as an example. The respiratory motion for this example case is shown in Figure 30.

Figure 29. Illustration of the determination of E and D.
Figure 30. A particular respiratory motion we designed to demonstrate the image quality difference between the two 4D-MRI techniques.

Breathing variation is a key factor that affects the image quality of 4D-MRI. Due to the difference in image acquisition scheme, the two 4D-MRI techniques (cine-mode and sequential-mode) are expected to have different yet unknown sensitivities to breathing variation. It is therefore of interest to study the effect of breathing variation on the image quality of 4D-MRI and compare it between the cine-mode and sequential-mode 4D-MRI techniques. To do this, we performed simulation studies using the XCAT digital phantom that was controlled by 20 different real cancer patients’ Real-time Position Management (RPM) breathing profiles. One example of the RPM signal is illustrated in Figure 31. It shows the beginning 75 seconds of the RPM signal of the first patient’s. Evaluating metrics $E_{\text{seq}}$ and $E_{\text{cine}}$ were derived from simulation 4D-MRI; $D_{\text{seq}}$ and $D_{\text{cine}}$ were derived for each RPM breathing profile and were compared between the cine-mode and the sequential-mode using the Wilcoxon Signed Rank test.
Furthermore, to systematically evaluate the relationship between breathing variation and 4D-MRI image quality, we constructed 500 irregular respiratory profiles with a wide range of breathing irregularities, which was defined as:

$$\text{Ir} = \sqrt{\left(\frac{\sigma_{\text{amplitude}}}{\overline{A}}\right)^2 + \left(\frac{\sigma_{\text{period}}}{\overline{T}}\right)^2}$$  \hspace{1cm} (1)$$

where \(\text{Ir}\) is the respiratory irregularity, \(\sigma_{\text{amplitude}}\) and \(\sigma_{\text{period}}\) are the variance of amplitude and period of each individual breathing cycle. \(\overline{A}\) and \(\overline{T}\) are the average amplitude and the average period of each breathing profile.

For a respiratory profile, each individual cycle on the profile will be assigned an amplitude value \((A_i)\) and a period time value \((T_i)\). There is a variation range for the \(A_i\) and \(T_i\). The range depends on the \(\text{Ir}\) of the respiratory profile. The value of \(A_i\) and \(T_i\) were randomly generated with a Gaussian distribution. The values of \(A_i\) subject to a Gaussian distribution of \(N(\mu=\overline{A}, \sigma=\sigma_{\text{amplitude}})\) and the values of \(T_i\) subject to a Gaussian distribution of \(N(\mu=\overline{T}, \sigma=\sigma_{\text{period}})\). The relationship between the \(\text{Ir}\) of the breathing profile and Gaussian distribution
parameters is showed in formula (1). We then determined $D_{seq}$ and $D_{cine}$ for each breathing profile using the method as mentioned above and studied the relationships between $D$ and $I_r$.

2.3.1.5. Healthy Volunteer Study

To evaluate our phase sorting technique for 4D-MRI, 12 healthy volunteers (6 females and 6 males) were enrolled in an IRB-approved study. 4D-MRI image acquisition was performed employing the HASTE/SSFSE sequence. The image acquisition mode was sequentially acquiring 2D MR images for volume of interest, and then repeating the volumetric acquisition for a pre-set number of times, which is pre-estimated as described in section II.C. Single-slice cine MR images were also acquired in the axial, coronal, and sagittal planes across the center of the critical structure (vessels in liver), providing an estimate of ground-truth of respiratory motion for comparison. All images were acquired in a 3 T Siemens clinical scanner. The subjects were positioned head-first-supine with arms down in the absence of immobilization devices and were instructed to keep normal respiration during the scans. Imaging parameters involved were: TR/TE, 975 ms/59 ms; FOV, 350x317.19 mm; flip angle, 115°; slice thickness, 5 mm; matrix, 256x232; bandwidth, 781 Hz/pixel. Healthy volunteers had different total number of slices. The range of the total number of slices was chosen to range from 15 to 35, and average total number of slices was 28±5. The numbers of repetition for all healthy volunteers were estimated based on the simulation (described in section II.C) results and imaging parameters ($N_R$, $N_S$, $N_B$) used for each healthy volunteer. Imaging frame rate was approximately 2 f/s. Breathing signals were recorded during image acquisition using Siemens’ Physiological Monitoring Unit (PMU) system with the bellows wrapped around the abdominal region. The sample rate was 50 Hz.
In our case, the computer drive PMU was the same with the one connected to the MR scanner, so MR image acquisition time can be synchronized with the time information recorded in the logging file generated by PMU. The PMU data logging was initiated manually via commands to the PMU/scanner computer before the sequence run. Time stamps in the header of the PMU log file were used to associate the PMU trace with the 2D image acquisition times, which was recorded in the header of image file. 4D-MRI were reconstructed using the result-driven, retrospective sorting technique described earlier in section II.A. The total number of 4D-MRI phase bins was selected to be 6 for all healthy volunteers. Tumor motion trajectories in the SI, AP, and ML directions were determined from 4D-MRI and compared with those from single-slice cine MR images, which served as references. On single-slice cine MR images, the same ROIs were tracked as on 4D-MRI. The ROI motion in SI and AP directions was tracked on sagittal cine, and its motion in ML direction was tracked on coronal cine. These tracking cine planes were selected because they have less inter-plane motion.

2.3.2 Results

2.3.2.1. Digital Phantom Validation Study

The 4D reconstruction results for ascending, interleaved, descending image acquisition modes are very similar. Nearly no obvious difference can be observed from the image. Figure 32 shows the simulated ‘4D-MRI’ (only phase 5 is shown as a representative) for ascending mode of the XCAT phantom and its comparison with the original 4D XCAT phantom. The two image sets in general matched well; only minor differences were found at the edge of organs, as shown in Figure 32 (c, f, e). The comparison of motion trajectories of the hypothesized tumor on
reconstructed 4D-MRI and average respiratory curve calculated from input are shown in Figure 33. Those measured from reconstructed 4D-MRI matched well with the input motion profile: the mean (±SD) relative amplitude error in motion amplitude is 2.7(±2.9) % in SI direction and 3.4 (±3.0) % in AP direction.

Figure 32. Reconstructed 10-bin T2-weighted 4D-MRI (only phase 5 is shown as a representative) simulated with XCAT phantom in axial (a), sagittal (d) and coronal (g) view, in comparison with the original 4D XCAT images (b, e and h). The differences between the two are shown in panel (c), (f) and (i) respectively. This is the XCAT simulation results where breathing motion was strictly regular and the data sufficiency condition was met. The total number of repetition ($N_r$) was set as 30 for the simulation scan.
Figure 33. Motion trajectories comparison of the hypothesized tumor in SI and AP direction. This is the XCAT simulation results where breathing motion was strictly regular and the data sufficiency condition was met.

2.3.2.2. Digital Phantom Studies of Variable Breathing: Data Completeness and Impacting Factors

As expected, the percentage of data completeness increases as $N_R$ increases, as shown as an example in Figure 25. The relationship between the two can be best fitted by an inverse exponential function (formula [8]). Figure 34 shows the average curves with error bars of the percentage of data completeness as a function of $N_R$ on average of 29 patients for three acquisition modes: ascending (a), descending (b), and interleaved (c). It was found there is no difference in the relationship between the three acquisition modes. The best function to describe the relationship was found to be:

$$C_P=100 \times (1-e^{-0.18 \times N_R}), \text{ when } N_S=30, N_B=6$$

[8]
According to the function, it can be seen that 100% data completeness would require a very large value of \( N_R \). In practical, missing a very small percentage of data does not cause clinically significant differences. From the relationship between error in tumor motion measurement and the percentage of data completeness derived, the error decreases as the percentage of data completeness increases, and reaches a stable stage at approximately 95% of data completeness, as shown in Figure 35 for both regular breathing motion (a) and patients' breathing motions (b). Both regular breathing motion case and patients' breathing motion case indicates that 95% of data completeness, labeled as \( N_{R, 95} \), is sufficient for 4D-MRI image acquisition. We therefore define \( N_{R, 95} \) as the number of repetition needed for 4D-MRI image acquisition.
Figure 34. Completeness curve for 29 patients in 3 acquisition modes: (a) ascending, (b) descending, and (c) interleaved. Acquisition mode does not affect the completeness of 4D dataset acquisition. This is the simulation result using 29 patients' RPM breathing traces.
Figure 35. Relationship between percentage of completeness ($C_p$) and the relative amplitude error of tumor trajectory in SI direction. These figures show XCAT simulation results using (a) strictly regular breathing motion, and (b) 29 patients’ breathing profiles. In both cases, the relative amplitude error decreases as the percentage of data completeness increases, and reaches a stable stage at approximately 95% of data completeness.

The relationships between $N_{R_{95}}$ and affecting factors ($N_B$, $N_S$, $P_0$, $B_P$, $B_V$) were further investigated and are illustrated in Figure 36. It was found that $N_{R_{95}}$ has a linear relationship with $N_B$, and is nearly independent of $N_S$ and $P_0$. There is a slight trend that $B_P$ is positively correlated with $N_{R_{95}}$, but no clear correlation between $N_{R_{95}}$ and $B_V$. 
Figure 36. (a) $N_{R, 95}$ is independent of $N_s$; (b) $N_{R, 95}$ is independent of $P_0$; and (c) linear relationship between $N_{R, 95}$ and $N_B$. (d) $N_{R, 95}$ is not significantly affected by the irregularity of respiratory. Specifically, in figure (a)-(c), 29 patients’ breathing profiles were used to statistically analyze the relationship between the parameters. However, in figure (d), 2500 simulated respiratory profiles with different $B_P$ and $B_V$ have been generated to test the relationship between breathing irregularity and $N_{R, 95}$. 
2.3.2.3. Comparison of Cine and Sequential Image Acquisition Modes

Figure 37 shows an example of a six-phase 4D-MRI data sorting results for the cine and sequential image acquisition modes. The solid curves represent the average breathing curve. The dashed curves represent the sorted breathing cycles of different slice locations. It can be seen that sequential-mode resulted in more consistent breathing cycles among different slice positions than the cine-mode, indicating potentially better 4D-MRI image quality and more accurate respiratory motion measurement with sequential-mode acquisition.

Figure 37. Example of 4D-MRI data sorting results for the cine-mode (a) and the sequential-mode (b) image acquisition. The black solid curves represent the average breathing curve. The dashed curves represent the sorted breathing cycles of different slice locations.

The example of 4D-MRI images reconstructed using the technique with cine image acquisition mode and the technique with sequential image acquisition mode are displayed in
Figure 38. The respiratory motion for this example case is shown in Figure 30. The comparison shows the image quality difference between using the two techniques.

Figure 38. An example of 4D-MRI images reconstructed using the technique with cine image acquisition mode and the technique with sequential image acquisition mode. White arrows pointed out some image quality differences showed between 4D-MRI reconstructed using the two techniques.

Figure 39 shows the comparisons between the cine-mode and the sequential-mode for evaluating metrics E (a) and D (b) from the XCAT phantom study. It can be seen that tumor motion measurement was significantly more accurate in the sequential-mode than in the cine-mode: the mean $E_{\text{cine}}$ was 0.12 cm and the mean $E_{\text{seq}}$ was 0.10 cm (p-value=0.02). Furthermore, the mean $D_{\text{cine}}$ was 0.47 cm and mean $D_{\text{seq}}$ was 0.24 cm (p-value<0.001), indicating the overall image quality of 4D-MRI is better in sequential-mode than in the cine-mode.
Figure 39. Comparison between the cine-mode and the sequential-mode for E (a) and D (b) from the XCAT phantom study.

Figure 40 shows the relationships between Ir and D derived using the 500 irregular breathing profiles for the cine-mode (triangles) and sequential-mode (circles). The image data acquisition completeness for different Ir with cine-mode (squares) and sequential-mode (diamonds) are also illustrated on the figure as references. It was observed that $D_{\text{cine}}$ is consistently larger than $D_{\text{seq}}$; and $D_{\text{cine}}$ increases faster as Ir increases than $D_{\text{seq}}$. Linear regression resulted in $D_{\text{seq}} = 0.47 \times \text{Ir} + 0.23$ and $D_{\text{cine}} = 1.17 \times \text{Ir} + 0.23$. Based on our measurement of 167 cancer patients’ breathing profiles, and the median breathing Ir value is 0.39. The Ir values distribution is shown below in Figure 41. The median value and the distribution imply that the sequential-mode would generally provide better image quality of 4D-MRI than the cine-mode. It is worth notice that when Ir is very small, $D_{\text{seq}}$ could be higher than $D_{\text{cine}}$ and $D_{\text{seq}}$ decreases as Ir increases. This was in fact caused by data insufficiency in the
sequential-mode, as indicated by its data completeness curve. When Ir is small, i.e., breathing is more regular, it takes longer time to acquire all necessary data to meet the DSC for the sequential-mode 4D-MRI, i.e., the image data acquisition completeness is low. Conversely, DSC for the cine-mode 4D-MRI can be easily met by setting the cine-duration longer than one breathing period.

![Figure 40](image.png)

**Figure 40.** Relationship between D and Ir. Linear regression resulted in $D_{\text{seq}} = 0.47 \times \text{Ir} + 0.23$ and $D_{\text{cine}} = 1.17 \times \text{Ir} + 0.23$. 
Figure 41. Ir values distribution measured from 167 cancer patients’ RPM breathing profiles.

2.3.2.4. Healthy Volunteer Study

Figure 42 illustrates an example of the breathing signal and the data completeness curve from a representative subject. Figure 43 shows the 6-phase 4D-MRI images in the axial (a), sagittal (b) and coronal (c) views of the representative, healthy volunteer No. 5. Reconstructed coronal 4D-MRI images of him generally matched well with coronal cine MR images, as illustrated in a Figure 43(c) and (d). ROI tracking has been measured on both reconstructed 4D-MRI and coronal cine MR for comparison. The trajectories are shown in Figure 44. The error bar shows the motion range of one critical structure (vessel) measured on
cine MR at different breathing cycles for each respiratory phase. The absolute motion trajectory amplitude error for this representative healthy volunteer is 2.0±1.2 mm. For all 12 healthy volunteers, 4D-MRI was reconstructed to 6 phase bins. Based on the data completeness and impacting factors simulation results, \( N_R \) was only affected by \( N_B \). Since we set \( N_B \) as 6 for all healthy volunteers, according to Figure 36(c), \( N_R \) was set to be about 20. The range of \( N_R \) was selected to range from 15 to 30, and average \( N_R \) was 20±4. Image acquisition modes included all 3 available modes (ascending, interleaved and descending). In summary, the average 4D reconstruction final completeness is 96.2±3.5; the average scanning time required for 6 bin reconstruction is 15.8 repetitions, which matched with the results from digital phantom study. Average absolute motion trajectory amplitude error is for all healthy volunteers is 2.5±0.3 mm.

Figure 42. (a) Part of the relative respiratory amplitude signal measured by bellows system. Phases were calculated according to the amplitudes. (b) completeness curve for one representative healthy volunteer, with total 20 slices, 20 measurements, 6 phase bins and maximum 99.1667% completeness. Scanning time required for 4D reconstruction is 14 repeated scans of volume of interest.
Figure 43. Reconstructed 4D-MRI for one represent healthy volunteer in axial view (a), sagittal view (b), coronal view (c) and in comparison with T2-weighted cine in coronal view (d).

Figure 44. Critical structure trajectories from 4D-MRI matched well with those from single-slice cine MR. The error bar shows the motion range of one critical structure (vessel) measured on cine MR at different breathing cycles for each respiratory phase. This figure shows the results of one representative healthy volunteer.
Chapter 3: Development of k-space-based retrospective 4D-MRI technique

3.1 Development of a 2D k-space sorting technique using a T2-weighted MRI sequence

In order to overcome the limitations of current retrospective 4D-MRI techniques, and allow MRI sequences with high tumor-tissue contrast but low frame rate to be used for 4D-MRI, we report here a novel strategy which is based on k-space reordering for retrospective 4D-MRI. Unlike previous retrospective 4D-MRI techniques where sorting is performed on images (labeled as image-based sorting in this paper), the new technique reorders the k-space of MR images based on respiratory information, allowing for finer segmentation of data in the time domain. This technique eliminates the necessity of fast 2D MR imaging for retrospective 4D-MRI, and enables potential improvement in temporal and spatial resolution of 4D-MRI. Several groups have recently studied motion correction methods. Hansen et al used a non-rigid registration algorithm to generate deformation maps between different respiratory phases, and applied them to each cardiac cycle image to correct respiratory motion\textsuperscript{44}. Similarly, Odille et al developed a frequency domain-based reconstruction framework for correcting motion artifacts of MR images. This particular method employed an optical flow-based motion model to determine phase information of k-space data\textsuperscript{45}. However, this study focused on MR motion correction used in a traditional radiology perspective. It concerns only one respiratory phase and the result is a single 3D MR dataset. The study’s main goal is to achieve high image quality for a single phase,
while motion information from other phases is minimized. The reconstruction framework and motion model used are designed for this specific purpose, which is greatly different from respiratory motion management associated with 4D-MRI. Moreover, Akçakaya et al investigated a k-Space-Dependent respiratory gating technique where the center of k-space is gated using respiratory navigators to generate three-dimensional flow imaging. However, that technique uses prospective gating, where image data will only be acquired when the motion reaches a certain phase. The gating requires hardware adjustments on the MR scanner. 4D-MRI requires a systematic approach capable of (a) handling patient breathing irregularities, (b) maximizing MR image quality, and (c) improving motion information accuracy at each phase, while (d) minimizing adverse influence from breathing variation. In this study, we present a retrospective 4D-MRI k-space reordering technique for respiratory motion. Contrary to prospective gating, retrospective sorting methods continually acquire image data and sort them based on synchronized motion signals from a surrogate. In this paper we explain the principle of k-space reordering and demonstrate its feasibility for 4D-MRI application using the digital human phantom XCAT and human subjects.

3.1.1 Research approach

3.1.1.1. Retrospective 4D-MRI with k-space Reordering

Similar to image-based retrospective 4D-MRI, k-space sorting 4D-MRI also requires a breathing signal that is synchronously recorded during image acquisition. However, unlike image-based 4D-MRI that assigns a respiratory phase/amplitude to each MR image, the new technique assigns a respiratory phase/amplitude to each k-space line or segment (a group of
lines) based on the recorded respiratory signal. The sampling rate of the respiratory signal should be much higher than the MR imaging frame rate to allow for fine segmentation of the k-space. MR image acquisition of the entire scanned volume needs to be repeated for a number of times in order to achieve data sufficient condition of 4D imaging, i.e., k-space data of all respiratory phases are acquired. For reconstruction, k-space data will be re-binned based on respiratory phases, and the reordered k-space will be used to generate 4D-MRI.

In principle, the concept of retrospective k-space reordering can be applied to a variety of standard MR sequences, either 2D or 3D, using cine, sequential, or interleaved slice acquisition ordering, given that the respiratory status of k-space lines/segments can be accurately determined. In this paper, we demonstrate this technique on the 4D-XCAT human phantom using a 2D single-shot echo planar imaging MRI sequence in sequential 2D image acquisition mode. The sequential 2D image acquisition mode sequentially acquires 2D MRI images for each slice location (slice 1, slice 2, slice 3...). The k-space acquisition scheme for ky lines was also sequentially acquired, i.e., ky-lines were acquired from line 1 to line 256 within k-space. Figure 45 shows the schematic plot of k-spacing reordering and image reconstruction based on the multi-shot fast spin echo (FSE) sequence. The k-space is divided into only four segments for demonstration purpose. Each k-space segment is assigned to a respiratory phase that is determined from the breathing signal. The k-space is then re-binned based on respiratory phases, and finally the reordered, phase-specific k-space is used to reconstruct 4D-MRI using 2D inverse fast Fourier Transform (iFFT).

An important challenge of the retrospective k-space reordering technique is the determination of the number of repetitions ($N_R$) that is needed to satisfy the data sufficient condition for 4D-MRI. Due to patients' breathing variations, the assignment of respiratory
phase to k-space segments is rather random, making it difficult to determine if data of all respiratory phases have been collected. To tackle this challenge, we performed computer simulations based on the assumption of a 2D multi-shot FSE MRI sequence, with a sequential 2D image acquisition mode, as well as a sequential ky-line acquisition scheme, to systematically study the relationship between $N_R$ and the percentage of data completeness ($C_P$), and the effects of potential influencing factors: total number of slices ($N_S$), total number of respiratory phase bins ($N_P$), the number of k-space segments ($N_{KS}$), image frame rate ($F$), MR image spatial resolution ($R$), and initial respiratory phase at image acquisition ($P_0$). A total of 30 cancer patients’ respiratory profiles were used in the simulation study.
Figure 45. Illustration of the process of retrospective 4D-MRI based on k-space reordering. Respiratory phase of each k-space segment is determined from the breathing signal that is acquired synchronously during image acquisition. K-space reordering is performed so that segments of the same respiratory phases are grouped together. Respiratory correlated 4D MR images are generated by reconstructing each phase-specific K-space using iFFT.
3.1.1.2. Digital Phantom Study

To demonstrate the feasibility of retrospective 4D-MRI with k-space reordering, we performed a computer simulation study using the XCAT human phantom. The respiratory motion of the XCAT phantom is controlled by two regular motion profiles (period: 5 seconds): one is diaphragm motion in the SI direction (peak-to-peak amplitude: 30 mm), and the other is chest wall motion in the AP direction (peak-to-peak amplitude: 10 mm). There is no input motion signal in the ML direction. A hypothesized tumor (diameter: 40 mm) was placed in the middle of the liver and moved with the surrounding tissue (note that the liver is modeled to move as a whole in the XCAT phantom, so the hypothesized liver tumor moves in the same manner as the input diaphragm and chest wall motions). XCAT images were generated using the following parameters: resolution of 256x256, pixel size of 2.5x2.5 mm, and slice thickness of 3 mm. Organ intensities in the XCAT images were set as in T2-weighted MR images.

Image acquisition and subsequent k-space reordering were mimicked by the computer simulation using a 2D multi-shot FSE sequence with sequential acquisition mode. Assuming a frame rate of 0.448 f/s, it will take 2.23 s to acquire a 2D image, or 8.7 ms to acquire a k-space line (as we assumed 256x256 resolution). Based on that, a XCAT volumetric dataset covering the entire liver was generated every 8.7 ms, representing an ultra-fast snapshot of the XCAT phantom at a particular respiratory phase. For a 5 s breathing cycle, this resulted in a total of 574 complete XACT volumetric datasets. From each XCAT dataset, a 2D axial slice was extracted, where the location of the slice cycled from top to bottom of the XCAT volume from one XCAT dataset to next. The 2D axial slice underwent FFT to generate its corresponding k-space, which was then evenly divided into 16 segments. Each segment, which contained 16
adjacent k-space lines, was assigned a single respiratory phase based on the breathing curve. The above-described process was repeated for all XCAT datasets, generating a large number of k-space segments at different slice locations and covering different respiratory phases. These k-space segments were then reordered per slice location and per respiratory phase. In case of missing phases, the k-space segment data acquired at the same slice location and nearest respiratory phase will be used as a replacement. Finally, the reordered k-space data were used to reconstruct 4D images using iFFT. In this simulation, the number of respiratory phase bins was set to 10.

Image quality of the simulated ‘4D-MRI’ of the XCAT phantom was qualitatively evaluated. Image noise and SNR were measured for each respiratory phase, and Image quality was compared with the simulated ‘4D-MRI’ reconstructed from the image-based sorting method. Tumor motion trajectories were determined from the ‘4D-MRI’ and compared with the input signals. Mean absolute amplitude difference (D) and cross-correlation coefficient (CC) between the two were calculated.

### 3.1.1.3. Healthy Volunteer Study

One healthy volunteer was prospectively enrolled in an IRB-approved study. A multi-shot 2D FSE MR sequence was employed with interleaved slice acquisition ordering (slice 1, slice 3, slice 5..., and then slice 2, slice 4, slice 6...) for 4D-MRI reconstruction. All images were acquired in a 3.0T GE clinical scanner (General Electric, Waukesha WI, USA), with a frame rate of about 7 seconds per frame. The subject was positioned head-first-supine with arms up. No immobilization device was used, and the patient was instructed to breathe normally during the
acquisition. A volume near the diaphragm was chosen as the imaging volume and scans were repeated 20 times in order to ensure sufficient data was collected for each respiratory phase. Imaging parameters were: TR/TE, 3750 ms/101 ms; FOV, 400×400 mm; slice thickness, 8 mm; matrix, 256×256; number of segments, 16; echo train length, 16; bandwidth, 195 Hz/pixel; number of slices, 9. The Bellows system wrapped around abdomen was used as an external surrogate indicating respiratory motion signal during image acquisition. The respiratory signal was recorded with a sample rate of 25 Hz and synchronized with k-space signal acquisition. Respiratory phases were calculated followed by 4D-MRI reconstruction. A 2D single-shot FSE MR sequence with the same scanning parameters was also employed on this healthy volunteer for the image-based phase sorting. The image quality of 4D-MRI reconstructed using the k-space reordering and the image-based phase sorting was compared.

3.1.2 Results

3.1.2.1. Data Completeness for k-space Reordering 4D-MRI

As expected, it was found that the greater the number of repetitions, the more complete the k-space data obtained for 4D-MRI, as shown in Figure 46(a). In sum of simulations using 30 cancer patients’ breathing profiles, the relationship between the two can be best expressed as an exponential function. When \( N_S = 30 \) and \( N_P = 6 \), the best fit is:

\[ C_p = 100 \left( 1 - e^{-0.18N_R} \right) \]

It can be seen that acquiring 100% of data would require a very large \( N_R \). In practical, missing a very small percentage of data (i.e., \( C_p \) is very close to 100%) may not cause any clinically significant differences in the integrity of 4D-MRI. As revealed in Figure 46(b), the
relative error in tumor motion measurement from k-space reordering 4D-MRI decreased as $C_P$ increases, and tended to stabilize after 90% of data completion. At $C_P$ of 95%, the relative error was 0.66%, indicating that $N_R$ at $C_P$ of 95%, labeled as $N_{R, 95%}$, is sufficient for k-space reordering 4D-MRI.

Figure 47 shows the relationships between $N_{R, 95%}$ and the potential influencing factors ($N_P$, $P_0$, $F$, $N_S$, $R$ and $N_{KS}$). $N_{R, 95%}$ was found to be approximately linearly proportional to $N_P$ ($r=0.99$), and nearly independent of all other factors. It should be noted that although $F$ and $N_S$ do not affect $N_{R, 95%}$, they will affect the total acquisition time of 4D-MRI ($T$) in the following manner:

$$T = \frac{N_{R, 95%} \cdot N_S}{F}$$  \[10\]

In addition, spatial resolution and temporal resolution are often constrains to each other in MRI. Increasing spatial resolution will decrease temporal resolution, and vice versa. As a result, $R$ will also affect the total acquisition time of 4D-MRI via its effect on $F$.

The derived relationships as shown above can be used to determine the minimum number of repetitions and the imaging time required for k-space reordering 4D-MRI. For example, for a 6-phase 4D-MRI with 30 slices, the number of repetitions needs to be 16 or greater in order to achieve at least 95% of the necessary data.
Figure 46. Results of study on data competition condition and its relationships with influencing factors for retrospective k-space reordering 4D-MRI: (a) relationship between $C_P$ and $N_R$, (b) relative error in tumor motion measurement as a function of $C_P$. 

Simulated data for 6 phase bins, 30 slices, 29 patients' breathing profiles
Fitting curve: $y = 100(1 - \exp(-0.18\times x))$

Fitting curve:
$y = 1.8\exp(-0.057\times x) + 5\exp(-0.06\times x)$
Figure 47. The relationship between $N_{R, 95\%}$ and the following: $N_P$ (a), $P_0$ (b), $F$ (c), $N_S$ (d), $R$ (e), and $N_{KS}$ (f). $N_{R, 95\%}$ was found to be approximately linearly proportional to $N_P$ ($r=0.99$), and independent of all other factors.

3.1.2.2. Digital Phantom Study

Figure 48(a) shows the 10-phase ‘4D-MRI’ images of the XCAT phantom using the k-space reordering technique, where the respiratory motion can be readily seen in all three orthogonal views. This 4D-MRI data acquisition completeness reached 100%. On average, image noise is $3.0\pm1.0$ and SNR is $64\pm27$, using 10 respiratory phases. Tumor motion
trajectories measured from 4D-MRI matched well with the input signals, as shown in Figure 48(b). D was 0.83 mm and 0.83 mm, and CC was 0.998 and 0.992 in SI and AP directions, respectively. Figure 48(c) shows representative coronal images of the original XCAT phantom, the simulated ‘4D-MRI’ using image-based phase sorting technique, and the simulated ‘4D-MRI’ using the k-space phase reordering technique. The ‘4D-MRI’ using the image-based sorting technique showed a discontinuity (zig-zag artifacts) on the edges the tumor and organs. The ‘4D-MRI’ using the k-space reordering technique demonstrated much smoother edges, but increased background noise (indicated by arrows), presumably because there were some phase variations during k-space reordering and re-binning.
Figure 48. (a) 10-phase k-space reordering ‘4D-MRI’ images of the XCAT phantom. Dashed lines are added to assist the visualization of tumor motion. (b) Comparison of tumor motion trajectories between the ‘4D-MRI’ and the input signals. (c) Coronal images of the XCAT phantom illustrating the differences between the k-space reordered ‘4D-MRI’ and the original XCAT. Background noise is observed in the k-space reordered ‘4D-MRI’ (indicated by arrows).

The simulation studies suggested that it is feasible to generate respiratory correlated 4D-MRI by retrospectively reordering k-space based on respiratory phase. This new technology may lead to the next generation 4D-MRI with high spatio-temporal resolution and optimal tumor contrast, holding great promises to improve the motion management in radiotherapy of mobile...
cancers. We plan to conduct a healthy volunteer study to investigate the feasibility of the technique.

### 3.1.2.3. Healthy Volunteer Study

Figure 49 demonstrates the 6-phase 4D-MRI images in orthogonal views of the healthy volunteer. The diaphragm was chosen as the respiratory motion indicator. The slice locations of the sagittal and coronal views were selected to be near the center of liver. The 4D-MRI images successfully revealed the respiratory motion of the healthy volunteer. The most predominant artifacts showed on 4D-MRI images are the aliasing artifacts in the AP direction, induced by the tolerant motion range of each phase bin. This aliasing is minimal in coronal view. The average breathing period of the subject was 8 seconds, resulting in a data completeness of 96.27% for the 6-phase 4D-MRI.

Figure 50 shows coronal and sagittal images of the healthy volunteer using image-based phase sorting technique, and k-space reordering technique from one representative phase bin. Some discontinuity on the dome of the diaphragm (indicated by white arrows) can be observed compared to the 4D-MRI reconstructed with the k-space reordering technique, which demonstrated much smoother edges, but increased background noise. Both edge discontinuities demonstrated on image-based phase sorting 4D-MRI and increased background noise demonstrated on k-space reordering 4D-MRI are presumably induces by breathing variations.
Figure 49. Representative 6-phase 4D-MRI images of the healthy volunteer in the axial, sagittal and coronal views. All images are anatomically near the center of the liver.

Figure 50. Coronal and sagittal images of the 4D-MRI reconstructed using image-based phase sorting and the k-space reordering methods. Apparent tissue discontinuity on the dome of the diaphragm (indicated by white arrows) are observed on 4D-MRI reconstructed using image-based phase sorting, while 4D-MRI reconstructed using k-space reordering demonstrated much smoother edges.

3.2 Development of a 3D k-space sorting technique using a radial k-space acquisition MRI sequence

The method is based on a sequence providing T1-weighted MRI signal with 3D radial trajectory sampling 48. Each radial spoke readout data line in k-space will start from the 3D
center of Field of View (FOV). The radial spoke readout data lines are labeled as \( k(r,\phi_i,\theta_i,t_i) \), and the 3D center of FOV are labeled as \( k(0,0,0,t_i) \) in our study. \( k \) represents k-space and \( t_i \) represents the time when the radial spoke is acquired. Respiratory signal can be extracted from \( k(0,0,0,t_i) \). Since the respiratory signal is extracted from the k-space data itself, Respiratory signal and image data acquisition will be synchronized. Each \( k(r,\phi_i,\theta_i,t_i) \) data will be sorted based on its corresponding respiratory phase calculated from the extracted respiratory signal. 3D reconstruction will be conducted for each of the respiratory phase bins to generate the time resolved 4D-MRI images.

### 3.2.1 Research approach

As a feasibility study, this technique was implemented on the digital human phantom XCAT. The respiratory motion was controlled by an irregular motion profile. A 3D radial k-space data acquisition trajectory was used for sampling the datasets. Each radial spoke readout data line starts from the 3D center of Field-of-View. Respiratory signal was extracted from the center of k-space for each radial spoke of the 3D k-space data acquired, as elaborated and illustrated in Figure 51. According to extracted breathing signal, the corresponding respiratory phase of each k-space radial spoke was calculated. Subsequently, k-space radial spokes was re-binned based on its self-synchronized respiratory signal using phase sorting. The sorted k-space dataset was then regenerated with the k-space spokes of the same respiratory phases, followed by MR image reconstruction using Fourier Transform to generate the time-resolved 4D-MRI images. This process was repeated for each respiratory phase bin to generate 4D-MRI.
Figure 51. Illustration of extracting respiratory signal from the center of k-space for each radial spoke.

The respiratory motion of the XCAT phantom is controlled by an irregular motion profiles (as shown in Figure 52 red curve): maximum motion in the SI direction was 30 mm, and maximum motion in the AP direction was 10 mm. There is no input motion signal in the ML direction. A hypothesized tumor (diameter: 25 mm) was inserted in the lung and moved with the surrounding tissue. XCAT images were generated using the following parameters: resolution of 128x128x128, pixel size of 2.5x2.5x2.5 mm. To validate using signal extracted from k-space center data as a respiratory surrogate, we compared breathing signals determined from k-space center data with the input controlling breathing profile for XCAT. Relative amplitude error and phase error were calculated. Subsequently, 3D reconstruction was conducted for the sorted k-space data of each phase bin to generate 4D-MRI. In this simulation, the number of respiratory phase bins was set to 10.

Image quality of the simulated 4D-MRI of the XCAT phantom was qualitatively evaluated. Tumor motion trajectories were determined from the 4D-MRI and compared with the input signals. Mean absolute amplitude difference (D) between the two was calculated.
3.2.2 Results

Figure 52 shows a good match in normalized breathing signals between the signals extracted from k-space center data and the input controlling breathing profile of XCAT. The relative amplitude error was 8.6% and the relative phase error was 3.5%. As showed in Figure 54, 4D-MRI on digital phantom XCAT demonstrated a clear motion pattern with little serrated artifacts. Tumor motion trajectory measured from 4D-MRI in three directions were showed in Figure 53, with average XCAT input respiratory trajectory as a reference (red). D was 0.21 mm in SI direction, 0.23 mm in AP direction and 0.23 mm in ML direction.

Figure 52. Comparison of respiratory signals extracted from k-space center data (black) and the input controlling signal (red). Top row: normalized amplitude signal; bottom row: calculated respiratory phase information for the amplitude signal.

Figure 53. Tumor motion trajectories in three directions were measured. It is compared with average input respiratory trajectory of XCAT.
Figure 54. 4D-MRI reconstruction results with lung tumor using 3D k-space sorting technique.
Chapter 4: Development of diffusion-weighted 4D-MRI (4D-DWI) technique

4.1 Development of a retrospective 4D-DWI technique based on 2D interleaved slice acquisition ordering

It is well known that diffusion-weighted imaging (DWI) offers anatomical and functional information with excellent tumor-tissue contrast. It is an important auxiliary MRI weighting shows great promise for detection of pathology, cancer diagnosis, tumor target delineation, and cancer treatment assessment. Owning to its high tumor-to-tissue contrast and the advantage of not requiring exogenous contrast medium, it has been increasingly used in various clinical applications. DWI of the brain is a well-established and reliable imaging for assisting identifying, quantifying and evaluating many neurologic cancers. For abdominal cancers, DWI has also been shown to have superior tumor-to-tissue contrast as compared to CT, T1-weighted and T2-weighted MR images for cancer detection, especially with high b-values, as shown in Figure 55. High contrast of DWI leads to high sensitivity and specificity of DWI for detecting abdominal cancer. For example, DWI has a high accuracy (96%) in diagnosis of pancreatic cancer, similar to comprehensive MRI using multiple sequences (T1-, T2-, and contrast-enhanced perfusion MRI). In addition, as a functional imaging, DWI can be used for assessing treatment response and adaptive RT planning. However, respiratory motion in abdominal region largely decreases the quality of DWI images. Respiratory motion could induce substantial delineation and dose delivery errors in conventional radiation therapy for thoracic and upper abdominal cancers. In the recent a few decades, the developments of echo-planar imaging
(EPI)\textsuperscript{68}, high gradient amplitudes, multichannel coils, and parallel imaging\textsuperscript{69} have been instrumental to extend the applications of DWI to extra-cranial sites, including the abdomen and pelvis. For example, the introduction of parallel imaging enabled the reduction in the echo time (TE), the echo train length, and the k-space filling time, leading to substantially less motion artifact at image acquisition, thus enabling high-quality 2D-DWI images of the body to be obtained. Furthermore, Respiratory-Triggered DWI\textsuperscript{70, 71} and Breath-Hold DWI\textsuperscript{72} have been investigated for motion-artifact reduced 3D-DWI. Chen et al developed a high-resolution 3D-DWI for abdomen using multi-shot scan strategy and multiplexed sensitivity-encoding (MUSE). K-space data with the same respiratory amplitude were retrospectively combined for 3D reconstruction\textsuperscript{73}. Although the existing rapid imaging technique and breathing-hold technique help dealing with the respiratory motion, it does not provide comprehensive respiratory motion information for treatment of abdominal cancers.

![Figure 55. An example of pancreatic cancer tumor (white arrows) contrasts comparison between different images.](image)

The aim of this study is to investigate the feasibility of developing a novel diffusion-weighted 4D-MRI technique, namely 4D-DWI. To our best knowledge, 4D-DWI is new and has not been reported before. Compared to current 4D-MRI techniques, 4D-DWI offers unique
advantages in superior tumor contrast and capability of functional imaging. There are potentially a wide range of clinical applications for 4D-DWI in addition to radiotherapy, such as cancer detection and therapeutic response assessment.

4.1.1 Research approach
4.1.1.1 4D-DWI Technique

Our 4D-DWI technique was achieved by employing a fast echo-planar-imaging (EPI) 2D-DWI sequence to acquire axial images continuously throughout the breathing cycle under free breathing condition, and then retrospectively sorting the images separately in three diffusion directions based on the respiratory phases. 4D-DWI was generated by combining the sorted images in different diffusion directions. Image acquisition is performed by repeatedly imaging a volume of interest (VOI) using an interleaved slice acquisition ordering in the axial plane with multi-slice single-shot EPI 2D-DWI sequence under free-breathing condition. Each 2D-DWI image with an intermediately high b-value (b=500 s/mm\(^2\)) is acquired in x, y and z diffusion directions. Within one repetition, 2D-DWI images are acquired with interleaved slice acquisition ordering for the zero b-value, and then once for each of the three directions sequentially, that is, the images are acquired with a b-value of 0 (slice 1, 3, 5...2, 4, 6...), and then with an intermediately high b-value for x diffusion direction (slice 1, 3, 5...2, 4, 6...), for y diffusion direction (slice 1, 3, 5...2, 4, 6...), and then for z diffusion direction (slice 1, 3, 5...2, 4, 6...). No couch position movements are needed. Respiratory motion is simultaneously recorded along with image acquisition, using Physiologic Monitoring Unit (PMU) with a pneumatic device (a respiratory bellows) wrapped around the subjects’ upper abdomen as an external surrogate.
The synchronously respiratory signal is used in the retrospective phase sorting algorithm \(^{38}\) to generate 4D images using the following four 2D image datasets: the sets of data with the b-value of zero; the sets of data with the intermediately high b-value for x diffusion direction; the sets of data with the intermediately high b-value for y diffusion direction; and the sets of data with the intermediately high b-value for z diffusion direction. That is, the retrospective phase sorting algorithm is applied four times to sort the four datasets separately. For the first sorted 4D image dataset with a b-value of zero, it is labeled as 4D-DWI (b=0). For the three other sorted 4D image datasets with the intermediately high b-value, they are subsequently combined to reconstruct 4D-DWI (b=500 s/mm\(^2\)). The corresponding ADC maps for each respiratory phase bins is then calculated using 4D-DWI (b=0 s/mm\(^2\)) and 4D-DWI (b=500 s/mm\(^2\)). The process is illustrated in Figure 56. Cine MRI using steady state free precession (TrueFISP) \(^{23}\) is acquired as a reference showing respiratory motion.
Figure 56. Overall design of the 4D-DWI technique, including image acquisition scheme, reconstruction process.

4.1.1.2. Digital Phantom Study

The proposed 4D-DWI technique was first tested via computer simulation using the 4D XCAT human phantom. The respiratory motion of XCAT was programmed to be controlled by a given regular sinusoidal regular breathing profile (period: 5 s). The peak-to-peak motion amplitude of diaphragm in the SI direction were set to be 3.0 cm and chest wall motion in the AP direction was set to be 1.0 cm. no motion in lateral direction. The XCAT images were generated for abdominal region using the following parameters: in-plane resolution: 256x256; voxel size: 2.5 mm; slice thickness: 3 mm; one diffusion direction 2D image frame rate: 2.48 Hz. The XCAT
phantom was generated in the activity mode for DWI contrast image where the signal intensities of the organs and tissues were assigned using values measured from DWI images. Image noise was added to the XCAT DWI images to mimic the real DWI images with noisy background. A hypothesized spherical tumor of 20 mm in diameter was located in the head of pancreas.

The simulation was carried out in the following steps: 1) mimicking the image acquisition of DWI sequence in interleaved slice acquisition ordering by extracting axial 2D XCAT images from the 4D XCAT phantom for a VOI. The time of acquisition for each 2D image are recorded. The acquired images were then grouped to four image datasets based on the images’ b-value and the images’ diffusion direction; 2) repeating the acquisition process of VOI described in Step 1 for a number of times. The number of repetitions should be large enough to satisfy 4D sorting data completion condition \(^{15}\) for all four image datasets; 3) synchronizing the image acquisition time of each 2D image with the controlling respiratory motion signal, and acquiring respiratory phase information for each 2D image from the respiratory motion signal; 4) calculating the respiratory phase bin for each extracted 2D XCAT image; and 5) conducting the retrospective phase sorting to generate the simulated 10-phase ‘4D-DWI (b=500 s/mm\(^2\))’.

The respiratory motion on simulated ‘4D-DWI’ was quantified by extracting the motion trajectories of the hypothesized tumor in SI and AP directions. They were compared with input respiratory curve of XCAT. Absolute amplitude difference between the two were calculated for each phase bins. The mean absolute amplitude difference (D) was calculated to quantitatively evaluate the accuracy of the respiratory motion demonstrated on 4D-DWI.

In addition, to demonstrate the influences of 4D sorting on image quality, a heterogeneous tumor was inserted to the liver of XCAT as the Region of Interest (ROI). Other imaging parameters were the same as the previously described XCAT phantom studies. Using
the same image acquisition and reconstruction process, we generated 4D-DWI images of the heterogeneous tumor for $b=500 \text{ s/mm}^2$ and $b=0 \text{ s/mm}^2$ respectively. Free-breathing DWI was also simulated for the heterogenous tumor for comparison. Images of the static 3D tumor were used as the reference.

4.1.1.3. Human Subject Study

The proposed 4D-DWI technique was then tested on two healthy volunteers (1 female and 1 male, under a HIPAA-compliant IRB-approved study protocol with informed consent). For each subject, DWI sequence was employed with interleaved slice acquisition mode for the abdominal region from the dome of diaphragm to bottom of kidney. B-value was set to be 500s/mm$^2$ only for the first healthy volunteer. It was set to be both 0 and 500 s/mm$^2$ for the second healthy volunteer and the patient. Single-slice cine MR images were also acquired in the axial, coronal, and sagittal planes for the same field of view, providing ground-truth of ROI motion for comparison. All images were acquired in a 3T Siemens clinical scanner. The subjects were positioned head-first-supine with arms down without any immobilization device. They were instructed to breathe normally during the scans. Imaging parameters were: TR/TE, 6900 ms/61.2 ms; FOV, 380x285 mm; flip angle, 160°; slice thickness, 5 mm; matrix, 128x96; pixel spacing: 2.97x2.97; bandwidth, 2604 Hz/pixel. Imaging frame rate was ranges from 4-7 f/s. Siemens’ Physiologic Monitoring Unit (PMU) system with the bellows wrapped around abdomen as an external surrogate indicating respiratory motion signal during image acquisition. The respiratory signal was recorded with a sample rate of 50 Hz and synchronized with DWI image acquisition. PMU was initiating manually by commenting on the computer controlling the MRI
scanner. 4D-DWI were reconstructed using the following steps: 1) acquiring 2D DWI images by repeatedly imaging a VOI using the interleaved slice acquisition ordering in the axial plane with multi-slice single-shot EPI 2D-DWI sequence under free-breathing; 2) recording the human subject’s respiratory simultaneously signal using the external surrogate PMU with the bellows; 3) synchronizing the image acquisition time of each 2D image with the controlling respiratory motion signal, and calculating the respiratory phase for each 2D image; and 4) conducting the retrospective phase sorting to generate the simulated 6-phases ‘4D-DWI (b=0)’ and 6-phases ‘4D-DWI (b=500 s/mm²)’;

Motion trajectories of defined ROI, right kidney of the healthy volunteers and the lung tumor of the patient, were extracted from 4D-DWI and compared with those obtained from the single-slice cine MR images (as a reference). D is calculated for each human subject using 4D-DWI images.

4.1.2 Results

4.1.2.1. Digital Phantom Study

Figure 57(a) shows the simulated 10 phase ‘4D-DWI’ of the XCAT phantom. The comparison of motion trajectories of the hypothesized tumor on reconstructed 4D-DWI and XCAT input respiratory curve shown in Figure 57(b). Tumor trajectories measured from simulated XCAT 4D-DWI were consistent with the input signal: D is 1.88 mm in SI direction and 0.36 mm in AP direction.
Figure 57. (a) Reconstructed 4D-DWI simulated with XCAT phantom in axial, sagittal and coronal view. (b) The difference between tumor trajectories on 4D-DWI (black) and input respiratory curve (gray) in SI and AP directions.

Figure 58 shows the DWI for the XCAT heterogeneous liver tumor with regular respiratory motion. To simplify the image quality demonstration and analysis, only the sagittal view of the moving liver tumor region, the ROI, was shown in the figure. It shows the
comparison of 4D-DWI, free-breathing DWI and the original static 3D tumor inserted to the digital phantom.

Figure 58. Sagittal view of the simulated 6-phase 4D-DWI images, as compared to the simulated free-breathing DWI and the referencing static images of the heterogeneous XCAT liver tumor.

4.1.2.2. Human Subject Study

Reconstructed 4D-DWI of the human subjects also demonstrates the respiratory motion clearly. Figure 59 shows the 4D-DWI images of a representative healthy volunteer. The mean D values were 2.6 mm (SI) and 1.7 mm (AP) for the two healthy volunteers; and 1.6 mm (SI) and 1.4 mm (AP) for the patient.
Figure 59. (a) Reconstructed 6-phase 4D-DWI images and (b) the motion trajectories of “right kidney (ROI)” for one representative healthy volunteer.

4.2 Initial evaluation of 4D-DWI for motion management and therapy assessment

Limitations of current 4D imaging techniques for radiotherapy planning includes the following: 1) 4D-CT is insufficient in providing high tumor-to-tissue contrast, particularly for abdominal masses, and 2) the existing breathing-hold, rapid imaging techniques that has been used to deal with respiratory motion can help but not comprehensively includes respiratory motion information to imaging. Diffusion-weighted imaging (DWI) has been shown to have superior tumor-to-tissue contrast as compared to CT, T1-weighted and T2-weighted MR images.
for cancer detection. Meanwhile, Apparent Diffusion Coefficient (ADC) map derived from DWI is an emerging tool for radiotherapy treatment assessment. This study aims at evaluating the effects of the four dimensional DWI (4D-DWI) technique on Apparent Diffusion Coefficient (ADC) measurement. Feature analysis has been conducted for the ADC measurements as a further evaluation of ADC maps measured from 4D-DWI.

4.2.1 Research approach

While DWI has been shown to have superior tumor-to-tissue contrast as compared to other imaging technologies for cancer detection, Apparent Diffusion Coefficient (ADC) map derived from DWI is an emerging tool for radiotherapy treatment assessment. The proposed 4D-DWI technique reduced the blurring artifacts of DWI images, so it may also have an influence on the ADC measurements. In order to investigate the effects that the 4D-DWI technique may induce to the ADC measurement with different breathing variations, it is worthwhile to calculate the corresponding ADC maps for 4D-DWI images. As a comparison, DWI with no motion correction (free-breathing DWI) as well as the corresponding ADC maps can also be reconstructed. First of all, ADC maps of the XCAT simulated heterogeneous liver tumor described in section II.B were calculated for each respiratory phase bins of 4D-DWI using the ‘4D-DWI (b=0)’ and ‘4D-DWI (b=500 s/mm²)’. Free-breathing DWI and the corresponding ADC maps were reconstructed as a comparison. To simplify the analysis process, only the moving liver tumor region, the ROI, was used for analysis. Then the simulation was repeated for the same heterogeneous liver tumor with different respiratory motion patterns. 10 liver cancer patients’ breathing profiles measured previously was used to control the respiratory motion of
the XCAT phantom. Same image acquisition and reconstruction process was simulated. For each breathing profile, mean ADC value (mADC) and entropy (E) of ROI were calculated for the ADC maps derived from each phase bin of 4D-DWI, as well as free breathing DWI. The reference of mADC and E value was calculated from the original static 3D tumor inserted to the digital phantom.

The ADC maps were also measured for the human subject study. Same ROI, the right kidney of the second healthy volunteer and the lung tumor of the patient were analyzed for the ADC maps. mADC and E of ROI was calculated.

4.2.2 Results

The ADC measurements results of XCAT tumor with regular respiratory motion were demonstrated in Figure 60 in the top row. The middle and bottom row shows the mADC and E values of tumor region for each ADC image dataset. On average of 6 phase bins, mADC value was $2.6 \times 10^{-3}$ mm$^2$/s. mADC value for free-breathing condition was $3.9 \times 10^{-3}$ mm$^2$/s. The ground-truth was $2.6 \times 10^{-3}$ mm$^2$/s. On average of 6 phase bins, E value was 0.25. E value for free-breathing condition was 0.75. The ground-truth was 0.24. The values of both metrics were much closer to the reference with the 4D technique.

The statistical feature analysis results of tumor region mADC and E are shown in Figure 61. On average for the 10 patients’ breathing profiles, the tumor region mADC value was $2.7 \times 10^{-3}$ mm$^2$/s with 4D-DWI and $4.3 \times 10^{-3}$ mm$^2$/s with free-breathing DWI, respectively. The tumor region E was 0.29 with 4D-DWI and 0.87 with free-breathing DWI, respectively. The
Wilcoxon Signed Rank test shows that ADC measurements were significantly more accurate with the 4D-MRI technique.

Figure 60. XCAT ADC measurements for the heterogeneous tumor with regular respiratory motion. The top row shows the comparison of ADC maps of 4D-DWI, free-breathing DWI and the reference: the original static 3D tumor inserted to the digital phantom. The middle and bottom row shows the mADC and E values of tumor region for each ADC image dataset.
Figure 61. Summary of XCAT phantom mean ADC value and entropy calculated using 10 patients’ breathing profiles. The values measured from the corresponding ADC maps of 4D-DWI, free-breathing DWI and reference was illustrated. Wilcoxon Signed Rank test shows that mean ADC value and tumor entropy calculated from 4D-DWI were significantly more accurate than that from free-breathing DWI.

On average of 6 phase bins, mADC of ROI calculated from 4D-DWI (the healthy volunteer: $1.5\times10^{-3}$ mm$^2$/s; the patient: $1.7\times10^{-3}$ mm$^2$/s) were smaller than mADC of ROI calculated from free-breathing DWI (the healthy volunteer: $1.7\times10^{-3}$ mm$^2$/s; the patient: $2.2\times10^{-3}$ mm$^2$/s). On average of 6 phase bins, E of ROI calculated from 4D-DWI (the healthy volunteer: 1.08; the patient: 1.22) were also smaller than E of ROI calculated from free-breathing DWI (the healthy volunteer: 1.11; the patient: 1.35). The ADC feature analysis results have tallied in general with the XCAT simulation results.
Chapter 5: Summary and Future Plan

This dissertation was aimed at developing improved 4D-MRI techniques for motion management of abdominal cancers in advanced radiation therapy. More specifically, we wanted to achieve four goals in this development: 1) to improve the tumor to tissue contrast and 2) temporal-spatial resolution of 4D-MRI images; 3) to develop reliable and clinical reliable respiratory surrogate; and to 4) develop 4D-MRI that can provide functional information. The exploratory pathway of the development was illustrated in Figure 62. The research started from the 4D-MRI technique that uses body area of axial image acquisition as respiratory surrogate. The BA method was improved by applying it to sagittal image acquisition by reducing the phase-shift artifacts. However, both BA methods with axial image acquisition and sagittal image acquisition rely on motion mainly in the AP direction. To utilize motion information in the primary respiratory direction, the SI direction, we developed a new respiratory surrogate, namely SCD-Pol surrogate, for 4D imaging sorting. It was then found in our patient study that these 4D-MRI technique, although provide improved motion information, lack consistent performance in tumor contrast due to the use of the T2/T1-weighted MRI TrueFISP/FIESTA sequence. To achieve better tumor-to-tissue contrast, we subsequently further developed a 4D-MRI technique using a T2-weighted MRI sequence, in conjunction with a novel result-driven sorting method. As an extension of this work, we applied the same sorting method for 4D-MRI based on k-space reordering, for both 2D and 3D MRI sequences. In addition, we also explored the feasibility of diffusion-weighted 4D-MRI, or 4D-DWI, to achieve even higher tumor contrast. The effects of 4D-DWI on ADC measurement were also investigated.
In this dissertation, 4D-MRI methods were developed for different weighting mechanisms, including T2/T1-weighted, T2-weighted and Diffusion-weighted MRI, in conjunction with different retrospective sorting methods. A novel result-driven sorting method was also developed for 4D-MRI reconstruction. Phantoms (physical and digital) and human subjects were used in testing and validating these 4D-MRI techniques. It was found that the performance of 4D-MRI varied between different base sequences, and achieving high image quality in all concerning aspects was challenging. Overall, 4D-MRI has been shown to provide accurate respiratory motion measurement with improved (but varied) tumor contrast. Limitation of high frame rate requirement in retrospective 4D-MRI techniques was overcame by implement respiratory sorting and re-binning on k-space instead of image space. The k-space reordering method provided a potential solution to achieve both high spatiotemporal resolutions and high
tumor contrast. The computer simulation studies and human subject studies suggested that 4D-MRI image quality, especially spatio-temporal resolution can potentially be improved using the k-space sorting method. Furthermore, novel image-based respiratory surrogates were developed and evaluated on a 4D digital human phantom and human subjects.

The 4D-MRI techniques developed in this dissertation work can be categorized into three categories. Firstly, three image-based sorting 4D-MRI techniques were developed in the Aim 1. Secondly, two k-space sorting 4D-MRI techniques were developed in the Aim 2. Thirdly, 4D-DWI technique was developed and evaluated. Comparing these 4D-MRI techniques, the image quality they generated were different on several levels. The motion artifacts appeared as volume discontinuity on 4D-MRI generated using image-based sorting methods, while this volume discontinuity motion artifacts were shown on k-space using k-space sorting method. The k-space volume discontinuity motion artifacts were transferred to be volume blurring artifacts on the reconstructed 4D-MRI images, as shown in Figure 50. Comparing 2D k-space sorting with 3D k-space sorting, the transferring of volume discontinuity motion artifacts occurred not only in intra-plane space but also in inter-plane space. The 4D-DWI images were affected by the volume discontinuity motion artifacts as with image-based sorting 4D-MRI techniques. They were suffering from more several image distortion and image noise caused by the DWI sequence itself in addition to the motion artifacts.

Some of the 4D-MRI techniques developed in the dissertation were tested for feasibility with a limited number of human subjects. Future works include testing the developed 4D-MRI techniques on more human subjects, especially on cancer patients, to evaluate their clinical efficacy in different clinical settings. Statistical analysis with a large pool of patients should be conducted to compare image quality and accuracy of motion information between the different
4D-MRI imaging techniques. Studies on 4D-DWI with patients are expected to be potentially interesting, considering it (and the time-resolved ADC maps) can be used to more accurately extract radiomics for treatment response assessment and prediction.

4D-MRI techniques will be primarily used in clinic for delineation of mobile tumor 4D-MRI can yield better contours for tumor target as well as some normal tissues due to its superior tumor contrast to CT. As a result, 4D-MRI could lead to more appropriate treatment planning and more precise of treatment delivery eventually. Furthermore, the future plan can be to develop 4D-MRI based treatment planning and to evaluate its clinical impact in patient trials. MRI data reflects the magnetic properties of protons, and thus do not provide electron density information as CT does. Hence MRI cannot be used directly to calculate radiation dose in current radiation treatment planning system. The 4D-MRI based treatment planning system intended to create human organ and tissue atlas to correlate image intensities with CT image intensities for dose calculation. 4D-MRI based treatment planning utilizes more accurate tumor/organ volume and motion information comparing to that based on CT simulation. Thus it has the potential to increase the accuracy of treatment for radiotherapy of mobile cancers in the abdomen.
Reference


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Appendix

Publications


