4D-MRI for Motion Management in Radiotherapy

Erik Tryggestad
Assistant Professor
The Johns Hopkins University School of Medicine
Department of Radiation Oncology and Molecular Radiation Sciences
Outline

I: Introduction: 4D-CT deficiencies; motivations for/pitfalls of “4D-MRI”

II: Selection of prior 2D dynamic MRI (dMRI) in radiotherapy

III: Selection of prior 2D-4D dMRI in radiotherapy

IV: “4D-MRI” methods development at John Hopkins

V: Concluding remarks
Introduction: Deficiencies of 4D-CT
I Introduction: Deficiencies of 4D-CT, cont’d.

a) 4D-CT: End-Inhale

b) 4D-CT: Mid-Phase

c) 4D-CT: End-Exhale

Coronal

Sagittal
Introduction: Motivations for “4D-MRI”

• Non-ionizing, fast

• Allows for more complete motion characterization; likely can overcome pitfalls of 4D-CT, which represents a snap-shot in time and fails to address motion variability inherent to normal respiration

• Provides unique opportunities for validation studies of different management techniques (gating, breath-holding, tracking...)

• Offers possibilities for 4D tumor tracking as well as providing “representative” 4D anatomical imaging, as in 4D-CT

• Therefore, may be well suited for “4D” radiotherapy planning and further development

• Promises for MRI-guided RT: non-invasive real-time MR imaging of target will likely result in higher targeting accuracy and hence further margin reduction
Introduction: Pitfalls of “4D-MRI”

- Not widely available
- Cost-prohibitive?
- Geometric image distortions?
- Spatial resolution is more limited than CT (SNR tradeoffs)
- “4D-MRI” simulations likely take longer than present CT-based simulations
- Patient (dis-) comfort: body coils required are somewhat constrictive. MRI bores can cause claustrophobia (larger bore systems help)
- Not all patients can comply or are MRI-safe
- No standards for “4D-MRI”
- Therefore, no current support for “4D-MRI” in treatment planning systems

Early adopters must address these issues while demonstrating dosimetric/safety/clinical benefit
II. Review of selection of 2D dynamic MRI studies:

1. Lung: Koch et al. [IJROBP 2004; 60 (5): 1459]
2. Pancreas: Feng et al. [IJROBP 2009; 74 (3): 884]
3. Liver: Kirilova et al. [IJROBP 2008; 71 (4): 1189]
   [IJROBP 2007; 60(3): 895]
2D dMRI review: Koch et al. IJROBP 2004; 60 (5): 1459

- Thoracic 2D dMRI study in 3 volunteers and 4 lung cancer patients
- Skin markers monitored simultaneously with lung vessels on sagittal frames
- Cross-correlation-based vessel tracking

1.5 T (GE Signa)
- Fast gradient echo sequence
- TR: 4.0 ms; TE: 2 ms
- Flip angle: 60 degrees

Pixel size: 1.6² mm²
- Slab thickness: 10 mm
- Acq. speed: 450 ms/frame
- 100 frames per cine series
What is a “cross-correlation” in image processing?

Normalized cross-correlation:

\[ \text{ncc}_{k,N} = \frac{\sum_{i,j} (I_k \cdot I_N)}{\sqrt{\sum_{i,j} (I_k \cdot I_k) \times \sum_{i,j} (I_N \cdot I_N)}} \]
Conclusions:

- Best correlation observed between lung SI and mid-upper abdo skin
- Poorer lung-skin correlation in AP
- Significant inter-subject variability
- “Movement of an external fiducial may not correlate fully with, or predict, internal lung motion.”
II. Review of selection of 2D dynamic MRI studies:

1. Lung: Koch et al. [IJROBP 2004; 60 (5): 1459]
2. Pancreas: Feng et al. [IJROBP 2009; 74 (3): 884]
3. Liver: Kirilova et al. [IJROBP 2008; 71 (4): 1189]
   [IJROBP 2007; 60(3): 895]
2D dMRI review: Feng et al. IJROBP 2009; 74 (3): 884

- 2D dMRI Study in 17 unresectable pancreatic cancer patients
- Images obtained prior to and during chemo-radiation
- Simultaneous monitoring of diaphragm, abdominal wall and tumor borders to examine position correlations

Fig. 1. (A) The tumor is contoured on a coronal image. The superior and inferior tumor borders are marked, as is the diaphragm. (B) In addition to the tumor contour and superior and inferior borders, the abdominal wall is marked.

- 3 T
- Balanced fast-field echo
- Acq. speed: 333 ms/frame
- 1-minute continuous scanning
2D dMRI review: Feng et al. IJROBP 2009; 74 (3): 884

Conclusions:
• Pancreatic tumor motion is complex with high inter-subject variability
• Significant tumor deformation observed
• Abdominal wall and diaphragm are poor surrogates for tumor motion

Sensitivity: % of time beam was on when it should have been (tumor coverage)
Specificity: % of time beam was off when it should have been (normal tissue sparing)
Accuracy: % of time that both surrogate and tumor were in 10% range of motion gating window simultaneously
II. Review of selection of 2D dynamic MRI studies:

1. Lung: Koch et al. [IJROBP 2004; 60 (5): 1459]
2. Pancreas: Feng et al. [IJROBP 2009; 74 (3): 884]
3. Liver: Kirilova et al. [IJROBP 2008; 71 (4): 1189]
   [IJROBP 2007; 60(3): 895]
2D dMRI review: Kirilova et al. IJROBP 2008; 71 (4): 1189

- Study in 36 (primary and metastatic) liver SBRT patients
- Patients underwent 60 second flouro. to observe SI motion of diaphragm
- On same day, 2D dMRI in axial, sag and coronal planes to measure tumor motion
- Simple analyses of maximal tumor and diaphragmatic excursions

- 1.5 T (GE Signa)
- \( T_2 \) single-shot fast spin echo sequence
- TR: 1300 ms; TE: 90 ms
- Pixel size: \( 1.6^2-2.5^2 \) mm\(^2\)
- Slab thickness: 5 mm
- Acq. speed: 1 frame/sec.
- 60 seconds continuous acquisition
Conclusions:
- dMRI for radiotherapy is both feasible and non-invasive
- SI tumor motion (maximum amplitude) not well correlated with SI diaphragm motion (maximum amplitude)
II. Review of selection of 2D dynamic MRI studies:

1. Lung: Koch et al. [IJROBP 2004; 60 (5): 1459]
2. Pancreas: Feng et al. [IJROBP 2009; 74 (3): 884]
3. Liver: Kirilova et al. [IJROBP 2008; 71 (4): 1189]
   [IJROBP 2007; 60(3): 895]
2D dMRE review: Cai et al. PMB 2007; 52: 365

- 2D dMRI thoracic study in 3 volunteers
- Purpose was to examine (tumor) PDF stability/reproducibility given the potential application of the PDF in 4D RTP
- Scanned in sagittal plane at baseline and 2-3 weeks later
- 3 vessels (upper, middle and lower) tracked per subject

- 1.5 T (Siemens Sonata)
- TR: 105 ms; TE: 0.93 ms
- Flip angle: 52 degrees
- Pixel size: ≈2.6 × 1.7 mm
- Slice profile (~thickness): 7 mm
- Acq. speed: ≈ 10 frames/sec.
- 5 minutes continuous acquisition
- Cross-correlation based tracking
- Images up-sampled 5× for better tracking accuracy
**2D dMRI review: Cai et al. PMB 2007; 52: 365**

**Figure 3.** Absolute PDF reproducibility errors plotted as a function of MR scan time for each of the subjects. Measurement data are the mean over the three tracked lung vessels.

**Conclusion:**
Derived PDF not simply patient-dependent, but is also dependent on study time and frame rate.

**PDF Reproducibility Error as a function of frame rate:**

\[
\varepsilon(f) = \frac{\int |PDF_2(\delta, t, 10) - PDF_1(\delta, t, 10)| \, d\delta}{2} \times 100\%.
\]

**Figure 4.** Absolute PDF error plotted as a function of the imaging frame rate. Data are the average over all the tracked pulmonary vessels.

**Conclusions:**
- Derived PDF less dependent on frame rate than on scan time.
2D dMRI review: Cai et al. IJROBP 2007; 60(3): 895

- 2D dMRI study in 6 lung cancer patients and 8 healthy volunteers
- Sagittal scanning in a single slice for 5 minutes continuously
- 2D MIPs from full dMRI study were compared to derived 2D Internal Target Areas (ITA) for simulated cine-mode 4D-CT study
- Respiratory signal for “4D-CT” sorting was the tumor (patients) or a tracked vessel (volunteers)

- **1.5 T (Siemens Avanto)**
- **TrueFISP (or bSSFP) sequence**
- **TR: 105 ms; TE: 0.93 ms**
- **Flip angle: 52 degrees**
- **Pixel size: 1.5^2 mm^2**
- **Slice profile (~thickness): 7 mm**
- **Acq. speed: 3.33 frames/sec.**
- **5 minutes continuous acquisition**
Volunteers assuming 24 mm (diam.) circular tumor:

**Conclusions:**
- ITA from simulated 4D-CT 10-40% smaller than that from dMRI
- Clear dependency of ITA on breathing variability
- Situation may be worse than this in reality given that motion surrogates are used for commercial 4D-CT!

**Internal Target Area Error:**
\[
\epsilon = \frac{ITA_{RedCAM} - ITA_{dSGP}}{ITA_{dSGP}} \times 100\%
\]

**Breathing Variability from tracked motion trajectory:**
\[
\nu = \frac{STD(\text{peaks}) + STD(\text{valleys})}{2}
\]
III. Review selected studies where “4D-MRI” is derived using 2D slice-stacking:

1. Liver: von Siebenthal et al. [PMB 2007; 52: 1547]

3D dMRI review: von Siebenthal et al. PMB 2007; 52: 1547

• Multi-slice abdominal 2D dMRI study in volunteers demonstrating principle of navigator slice-based retrospective sorting to derive a “4D-MRI”

• 1.5 T (Philips Achieva)
• Steady-State Free Precession
• TR: 3.1 ms
• Flip angle: 70 degrees
• Pixel size: $1.8^2$ mm$^2$
• Slice profile (~thickness): 3-4 mm

• Acq. speed: 5.3-5.6 frames/sec.
  ➔ Effective acq. speed: 2.6-2.8 frames/sec.
• Sequential sagittal slice acquisition (with 22-30 slices)
• Continuous acquisition over tens of minutes
Each pair of consecutive or “embracing” navigator frames defines a liver “state” for sorting from which an entire 3D volume can be reconstructed.

Cost function:
combines template-matching derived shifts from navigator sub-regions

\[
c(i, j) = \sum_{r=1}^{P} \left\| \left( x_{j-1}^r - x_{i-1}^r \right) + \left( x_{j+1}^r - x_{i+1}^r \right) \right\| + \left\| y_{j-1}^r - y_{i-1}^r \right\| + \left\| y_{j+1}^r - y_{i+1}^r \right\|
\]

= \sum_{r=1}^{P} \left\| \Delta \tilde{X}_{r-1}^r + \Delta \tilde{X}_{r+1}^r \right\|
3D dMRI review: von Siebenthal et al. PMB 2007; 52: 1547

Simple navigator sorting based on 1D diaphragm

Proposed sorting method

Proposed method averaging over 5 best matching frames

Potential drawbacks:
- The dependency on the navigator may prolong the study

Conclusions:
- Provides a means for deriving high-quality “4D-MRI” for RTP that specifically addresses breathing motion variability
- One can simulate continuous/real-time 3D anatomic motion over the full imaged duration (at frame rate of navigator frames)
- If the goal is to derive a representative “4D-MRI” for planning (e.g., single-cycle 3D anatomic movie, as in 4D-CT), how does one define the set of reference navigator states?
- Surrogates for sorting have no direct extension to potential surrogates used for guidance of the therapy
III. Review selected studies where “4D-MRI” is derived using 2D slice-stacking:

1. Liver: von Siebenthal et al. [PMB 2007; 52: 1547]


• Comprehensive patient, phantom and volunteer study demonstrating feasibility of practical acquisition and sorting technique for representative “4D-MRI”
• 2D dMRI acquired axially – slice location incremented every ave. resp. period + 1 sec.
• Respiratory surrogate for sorting is image-based “Body Area” (BA)
• This surrogate first validated with 4D-CT data/images in patients

- Siemens Avanto (1.5 T)
- TrueFISP (bSSFP)
- TR: 3.6 ms; TE: 3.7 ms
- Pixel size: ≈1.4² mm²
Conclusions:
• Feasibility demonstrated
• No sequence development and no additional devices (for respiratory surrogate)

Questions:
• Unclear how the investigators deal with multiple images being available for a given phase and slice location since images acquired for longer than one breathing cycle, in general, per slice
• Does BA sorting work in coronal and sagittal orientations?
IV. 4D-MRI methods development at Johns Hopkins:

Method 1: 2D-to-4D sorting of dMRI to derive a representation of the subjects’ average breathing cycle

Method 2: 4D tumor tracking using orthogonal 2D dMRI slice planes

IRB-approved methods development study in volunteers underway

Collaborators:
Teboh Roland, Ph.D.
Russell Hales, M.D.
Todd McNutt, Ph.D
Joseph Herman, M.D.
John Wong, Ph.D.

Project receives personnel support from Siemens:
Steven Shea, Ph.D.
Aaron Flammang, Ph.D.
JHU method 1:

Goals:
• With clinical workflow and practicality in mind, develop methods to derive a robust, representative “4D-MRI” for direct application to RTP similar to present utility of 4D-CT

• This “4D-MRI” method should, in particular, address problems associated with variable breathing
JHU method 1: image acquisition

**TrueFISP (or bSSFP):**
- Stepped acquisition (slice 1, 2, 3...1, 2, 3)
- 2x2 mm² pixels in plane
- 5 mm slice profile
- Acquisition speed: 4 to 5 frames/sec (coronal and sagittal, respectively)
- Strong blood signal w/o contrast on board

**HASTE (Half-Fourier Single-Shot Turbo Spin Echo):**
- Interleaved acquisition (slice 2, 4, 6...1, 3, 5...)
- 2x2 mm² pixels in plane
- 5 mm slice profile
- Acquisition speed: 2.85 – 3.33 frames/sec.
  (coronal and sagittal respectively)
- Strong fat signal; good abdominal contrast
JHU method 1: simultaneous respiratory monitoring

Acquire external respiratory signal
(Physiological Monitoring Unit -- PMU)

PMU logging:
• synchronized with the image acquisition computer (well, in principle, anyway)
• auto started/stopped within sequence run
• sampled at ~50 Hz
JHU method 1: post-processing

In-house post-processing (MATLAB)

3D distortion correction

Analyze PMU trace to determine resp. bins

1st pass sorting: “Average” 4D-MRI

2nd pass sorting: “De-blurred” 4D-MRI

Derived 4D-MRI converted to DICOM

2nd-Pass Sorting:
- Retrospective slice stacking w/ 1st-pass employed
  for corresponding slice across all respiratory bins (within
  respiratory template) assigned to 3D recon associated with
  PMU respiratory bin (up to ~15 bins)
  - Each slice of given binned 3D recon is an average image over all available
    frames
  - Corresponding standard deviation image computed

1st-Pass Sorting:
- Retrospective slice stacking w/ 1st-pass employed
  - Raw frames, per slice location, assigned to 3D recon associated with
    PMU respiratory bin (up to ~15 bins)
  - Each slice of given binned 3D recon is an average image over all available
    frames
  - Corresponding standard deviation image computed
JHU method 1:

Analysis of PMU surrogate to determine respiratory intervals

- The “Moving Average” [Lu et al., Med Phys. 2006; 33 (10)] is quantified to aid in identification of maxima/minima.

- Amplitude binning is based on “Amplitude Probability” which is being explored to potentially improve the first-pass sorting.

Note: this method is an adaptation of that presented by Olsen et al. [IJROBP 2008; 70 (1): 243]
JHU method 1: Results for 1st-pass reconstruction

- bSSFP in lung volunteer (dark blood pulse on)
- 10-phase-bin reconstruction
- Average frames/bin/slice = 17
JHU method 1: Results for 1st-pass reconstruction

- HASTE in abdo volunteer
- 10-phase-bin reconstruction
- Average frames/bin/slice = 26
JHU method 1: 
1st pass result for amplitude-probability vs. phase binning

Slice 4/10
Slice 6/10
Slice 8/10

Phase
Amplitude-probability
JHU method 1:

Normalized cross-correlation based scoring to determine best matching frames for 2^{nd} pass reconstruction

- Clear indication of best matching phase (despite poor SNR in raw image in this case)
JHU method 1: Results for 2nd-pass reconstruction

- Ave 4D-MRI (ROI for NormXCorr)
- Ave 4D-MRI (Zoomed)
- De-Blurred 4D-MRI (Zoomed)

Slice 17/20

Slice 19/20

Average N = 30

N = 3

- bSSFP in lung volunteer (dark blood pulse on)
- Subject imaged for 30 minutes continuously
- 1st-pass result derived from respiratory phase binning
- 10-phase reconstruction
JHU Method 1: PMU QA

Frequently, the first-pass reconstructions are “garbage.”

→ Hypothesis to test was that the PMU clock synchronization is not reliable.

Derive respiratory trace from the diaphragmatic interface:

• Challenge: multi-slice study – diaphragm not consistent slice-to-slice
• Define rectangular ROI used in common over all slices
JHU Method 1: ex. case where PMU drifts temporally

- Sagittal lung bSSFP
- 10 slices for 13 minutes continuously

Challenging case to start because of breathing pattern
Assignment of maxima was not 100% robust
JHU Method 1: ex. case where PMU drifts temporally

- Raw PMU trace versus Diaphragm tracking result
  - @ start of acquisition
    - Out of phase!
  - PMU times scaled linearly by 1.003
  - @ end of acquisition
    - In Phase!
JHU Method 1: ex. case where PMU drifts temporally

without PMU time scaling:

uncorrelated!

with PMU time scaling (×1.003):

correlated!
JHU Method 1: diaphragm tracking indicates another challenge:

- Diaphragm position undergoing “baseline drift” over course of 30 minute study

Questions: Should the “representative” 4D-MRI image capture this drift? If so, how can we do this while preserving image quality?
Conclusions for JHU method 1:

• We have successfully demonstrated feasibility of this method in volunteers using two readily-available sequences

• Technique will be ready for prime-time when PMU issues are resolved

• Increased frame rates will allow us to scan commensurate anatomical volumes (as 4D-CT) in multiple orientations in a 30 minute MRI session (Acquisition speed over 20 frames/sec may be available for bSSFP)

• Although not yet explored, diaphragm signal or other similar image-based surrogates can be used as surrogate for sorting

• Having a long temporal sample capturing all manifestations of variability is good! However, it is unclear, e.g., how best to deal with baseline (diaphragm) shift that may occur
JHU method 2:

**Goal:**
Pre-treatment, perform “true” 4D tracking of the tumor (center of mass) using dMRI over a sufficiently long duration to adequately characterize motion (variability)

**Example Applications (not exhaustive list!):**
- Derive the “dynamic internal margin” Coolens et al. [PMB 53(16) 2008]
- Derive the spatial-3D probability density function for tumor motion
- Allow careful study of spatial-temporal correlations with traditional tumor motion surrogates such as an external respiratory trace or skin/surface markers
- Provide the necessary information to determine which potential breathing management strategy is best suited for the given patient, e.g., motion encompassing (ITV), probabilistic, gating, breath holding or tracking
JHU Method 2: image acquisition

Acquire orthogonal 2D (Sagittal + Coronal) dMRI
Siemens MAGNETOM Espree 1.5T

TrueFISP (bSSFP):
- interleaved acquisition (sag, coronal, sag...)
- 2x2 mm² pixels in plane
- slice thickness adjusted for motion out-of-plane
- Acquisition speed: ≈4 frames/sec.
JHU method 2: simultaneous respiratory monitoring

Acquire external respiratory signal (Physiological Monitoring Unit -- PMU)

PMU logging:
- synchronized with the image acquisition computer
- auto started/stopped within sequence run
- sampled at 50 Hz
Methods: post processing

In-house post-processing (MATLAB)

1. 3D distortion correction
2. 2D tracking on sag. and coronal planes, independently
3. 4D interpolation
4. Derivation of the DIM and 3D PDF
5. Spatio-temporal correlations with surrogates

4D sag/coronal tracking:
- User draws ROIs interactively looking at MIP images
- Sup.-inf. border of sag. and coronal ROIs is matched
- Based on ROIs, template images chosen from an arbitrary frame
- 2D normalized cross-correlation-based tracking/optimization
- Images up-sampled 4× to provide higher (spatial) tracking resolution

Work in progress!

Spatio-temporal correlations with surrogates
JHU method 2:
Example lung volunteer tracking result
JHU method 2:
Example lung volunteer tracking result, cont’d.

• Volunteer instructed to relax and breathe normally – breathing motion is highly variable
• Two discernable breathing modes detected
• In the “quiescent” state, the PMU correspondence is essentially lost
JHU method 2:
Example lung volunteer tracking result, cont’d.

• A typical 4D-CT scan may scan through the tumor in ~10 seconds
• Suppose we compare the full motion ITV vs. 10-second snapshot ITVs for a 1.5 and 3.0 cm (diameter) hypothetical GTV
JHU method 2:

Example lung volunteer tracking result, cont’d.

- A typical 4D-CT scan may scan through the tumor in ~10 seconds
- Suppose we compare the full motion PDF vs. 10-second motion trajectories:
JHU method 2: Example lung volunteer tracking result, cont’d.

Numerical 4D dose accumulation simulations

**Suppose** we “scan through” the tumor at times t=130-140 sec. and generate an ITV plan:

• GTV diameter = 1.5 cm

• PTV = ITV + 1 mm uniform expansion

• $D_{Rx, PTV} = 18$ Gy

• Quasi-realistic dose cloud: uniform in PTV; dose fall-off given by Gaussian tail with 3.5 mm sigma

• Assume “shift invariance”
JHU method 2: Example lung volunteer tracking result, cont’d.

• Numerical 4D dose accumulation simulations to illustrate utility

Suppose we now treat the patient over time, $t = 30-60$ sec:

- $D_{\text{min, GTV}} = 10.4$ Gy
- $D_{95} = 14.3$ Gy

DVH for GTV
JHU method 2: Example lung volunteer tracking result, cont’d.

• Suppose we now move our 10-second snapshot ITV target definition time window iteratively across the entire tracking duration.
• For each iteration perform a 4D dose accumulation for the dose cloud derived from the trial ITV (1.5 cm GTV) using the motion information from the entire duration.
Conclusions for JHU method 2:

• We have successfully demonstrated feasibility of this method in volunteers.

• Current focus is on finding practical ways to incorporate this information into clinical workflow.

• Truly 3D dMRI is highly desirable since additional information is available: e.g., tumor deformation can also be tracked and characterized; more complete study of potential internal/external surrogates can be performed. Tradeoffs between image quality and speed currently challenge this approach.

• There are likely ways to combine the method 2 with method 1 to derive a virtual representation of fully 4D tracking
V. Concluding remarks:

• Dynamic MRI has matured and is ripe for more widespread application in radiotherapy

• More investigation is needed to dosimetrically (and perhaps clinically) demonstrate that “4D-MRI” provides advantages over our present 4D imaging (4D-CT) so as to justify the required investments

  ➔ At Hopkins we soon hope to begin regularly scanning lung and abdominal patients with repeat 4D-MRI to estimate how robust the clinical 4D-CT-based plans are (dosimetrically speaking)

  ➔ Phantom studies planned also to evaluate the geometrical robustness of the dMRI sequences