Time-resolved volumetric MRI in MRI-guided radiotherapy: an in-silico comparative analysis

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Time-resolved volumetric MRI in MRI-guided radiotherapy: an in-silico comparative analysis

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Abstract

MRI-treatment units enable 2D cine-MRI centred in the tumour for motion detection in radiotherapy, but they lack 3D information due to spatio-temporal limits. To derive time-resolved 3D information, different approaches have been proposed in the literature, but a rigorous comparison among these strategies has not yet been performed. The goal of this study is to quantitatively investigate five published strategies that derive time-resolved volumetric MRI in MRI-guided radiotherapy: Propagation, out-of-plane motion compensation, Fayad model, ROI-based model and Stemkens model. Comparisons were performed using an MRI digital phantom generated with six different patient-derived motion signals and tumour-shapes. An average 4D cycle was generated as well as 2D cine-MRI data with corresponding 3D in-room ground truth. Quantitative analysis was performed by comparing the estimated 3D volume to the ground truth available for each 2D cine-MRI sample. A grouped patient statistical analysis was performed to evaluate the performance of the selected methods, in case of tumour tracking or motion estimation of the whole anatomy. Analyses were also performed based on patient characteristics. Quantitative ranking of the investigated methods highlighted that Propagation and ROI-based model strategies achieved an overall median tumour centre of mass 3D distance from the ground truth of 1.1mm and 1.3mm respectively, and a diaphragm distance below 1.6mm. Higher errors and variabilities were instead obtained for other methods, which lack the ability to compensate for in-room variations and to account for regional changes. These results were especially evident when further analysing patient characteristics, where errors above 2mm/5mm in tumour/diaphragm were found for more irregular breathing patterns in case of out-of-plane motion compensation, Fayad and Stemkens models. These findings suggest the potential of the proposed in-silico framework to develop and compare strategies to estimate time-resolved 3DMRI in MRI-guided radiotherapy.

Keywords: MRI-guidance, time-resolved MRI, organ motion, radiotherapy

1. Introduction

Magnetic Resonance Imaging (MRI) has recently become available as integrated image guidance modality in radiotherapy treatment units (Fallone 2014, Raaymakers et al. 2017, Keall, Barton and Crozier 2014, Mutic and Dempsey 2014, Lagendijk et al. 2014, Kashani and Olsen 2018). The intrinsic advantage of these machines is the ability to implement a full MRI-guided treatment workflow to allow direct target localization, which is particularly advantageous for sites affected by breathing motion, such as lung or liver (Bainbridge et al. 2017, Menten, Wetscherek and Fast 2017, Paganelli et al. 2018). Indeed, in-room MRI systems enable high quality MR imaging just prior to treatment (i.e. pre-beam imaging) and MR-guidance during treatment (i.e. beam-on imaging) for gating or tracking (Stemkens et al. 2016, Raaymakers et al. 2017, Kashani and Olsen 2018). However, the acquisition of 3D data with adequate signal-to-noise ratio (SNR), spatial and temporal resolution,
volumetric coverage and contrast is still a challenge for treatment guidance in the thoraco-abdominal site, being the acquisition time for fast 3D volumetric images currently on the order of seconds (Paganelli et al. 2018c, Stemkens, Paulson and Tijssen 2018). This motivated the implementation of respiratory-correlated 4DMRI strategies (Paganelli et al. 2015c, Von Siebenthal et al. 2007, Cai et al. 2011, Paganelli et al. 2018a, Stemkens et al. 2018) and novel MR sequences (Stemkens et al. 2018, Bruijnen et al. 2019), to enable both pre-beam anatomical and motion description and complement the clinical standard provided by 4D Computed Tomography (4D CT) (Boye, Lomax and Knopf 2013). Also, the use of fast 2D cine-MRI for organ motion quantification has been widely reported in the literature (Sawant et al. 2014, Koch et al. 2004, Plathow et al. 2004, Paganelli et al. 2015b, Seregni et al. 2017b, Fast et al. 2017, Paganelli et al. 2015a) and represents the current state-of-the-art method for real-time imaging in in-room MRI treatment systems. This practice is however limited to the acquisition of few 2D slices, which compromises an accurate adaptation for 3D motion.

For this reason, the ideal imaging strategy for in-room MRI treatment systems would yield real-time 3D information of both tumour and surrounding tissues, aiming at accurately tracking the tumour as well as describing organs at risk motion for retrospective dose accumulation (Stemkens et al. 2017, Stemkens et al. 2016, Stemkens et al. 2018, Paganelli et al. 2018c).

Several methods have been proposed in the literature to track tumour motion and derive its 3D local information based on 2D interleaved orthogonal cine-MRI slices (Kirilova et al. 2008, Bjerre et al. 2013, Brix et al. 2014). These approaches mainly assume a rigid description of the target motion, by acquiring a pre-treatment 3D scan, extracting a target template and performing template matching between the template and pairs of orthogonal 2D cine-MRI intersecting the target motion path. Recent studies investigated the non-rigid description of the target motion together with the estimation of the surrounding anatomy, relying on 3D or 4D pre-beam images, which are combined in-room cine-MRI data. The Propagation technique proposed by (Paganelli et al. 2018b) is an example of deriving the in-room 3D anatomical-pathological information by propagating the 2D non-rigid motion derived from orthogonal cine-MRI data in the three anatomical directions and using the derived volumetric motion field to warp a static 3D pre-beam volume. Alternatively, other methods exploit the motion information provided by 4D pre-beam imaging. One simple approach relies on estimating the out-of-plane motion not described in the cine-MRI by deriving the information from the motion of a prior 4D MRI (Seregni et al. 2017a). More intriguing approaches extended already proposed 4D CT global motion models, which rely on the correlation between the motion derived from a planning 4D CT and an in-room external surrogate (McClelland et al. 2013). The limitation of such methods is the well-known problem that the external surrogate may not be representative of the internal anatomical information. In the MRI-guided scenario, this issue is overcome by global motion models that make use of cine-MRI data as in-room information (Fayad et al. 2012, Stemkens et al. 2016, Harris et al. 2016, Garau et al. 2019).

The main drawbacks of the proposed strategies are related to the derivation of an accurate anatomical description for methods relying on the sole 3D pre-beam and beam-on cine-MRI images, and on the capability to estimate unseen motion for approaches built on 4D pre-beam imaging. Pros and cons of the above-mentioned techniques that derive time-resolved 3D information from 2D cine-MRI data have been therefore singularly investigated in separated studies, but a rigorous comparison between these approaches was never performed.

In this study we propose an in-silico comparison of five techniques presented in the literature to derive time-resolved volumetric MRI from 2D cine-MRI data, relying on a digital MRI phantom (Paganelli et al. 2017). The phantom represents an in-silico platform to simulate patient-specific pre-treatment 4D MRI and in-room cine-MRI data. This allows comparing different strategies for deriving time-resolved volumetric data for clinical applications, such as 3D tumour tracking and entire anatomy estimation. Quantitative ranking of the investigated approaches allowed us to provide a comprehensive evaluation in terms of patient characteristics, thus laying the foundations for preliminary suggestions for clinical applications.

2. Materials and Methods

2.1. Dataset
A digital anthropomorphic MRI phantom, which is the MRI version (Paganelli et al. 2017) of the extended cardiac-torso (XCAT) phantom (Segars et al. 2010), was used to simulate MRI data. The XCAT phantom was animated with free-breathing respiratory signals derived from six non-small cell lung cancer patients, leading to the generation of six different datasets. The breathing signals of each patient were obtained from an MR imaging session during which cine-MRI images were acquired in free breathing conditions over several respiratory cycles (~ 2/3 minutes) (Lee et al. 2016) (Table SI in supplementary materials). Signals from the chest, diaphragm and tumour were used to simulate antero-posterior (AP) abdominal motion, superior-inferior (SI) diaphragm motion and AP, SI and right-left (RL) tumour motion. Specifically, tumour motion was extracted from the centroid of the segmented tumour in cine-MRI data; the segmentation was performed by a region growing algorithm. Diaphragm motion was derived by means of a derivative function on the diaphragm region in cine-MRI; whereas external breathing motion of chest was monitored by the Siemens PMU belt. Signals were interpolated to achieve an acquisition time of 300ms (i.e. cine-MRI temporal resolution).

To simulate treatment planning conditions, the average cycle signal for each patient was determined as the mean values of the free-breathing signals over 10 respiratory phases and used to generate a 4D CT phantom featuring 10 respiratory bins. To simulate treatment condition, a temporal window lasting 9.6s and starting from the exhale sample closest to the exhale volume of the 4D CT was selected, thus generating approximately thirty-two 3D samples at the temporal resolution of 300ms, with range of motion higher than the average respiratory cycle. Table I reports the difference between the average cycle and the intra-treatment motion over the selected temporal window, in terms of range of motion and baseline difference. Additionally, the phantom reality was augmented by including the size and location of the patient-specific tumour segmented on the exhale phase of the patient’s 4DCT.

The obtained CT volumes were finally converted in terms of MRI data, simulating a T2/T1-weighted sequence (i.e. TrueFISP) through the MRI phantom CoMBAT (Paganelli et al. 2017). For details on simulated parameters, refer to Section 2.2. A 4D MRI pre-beam phantom and in-room 3D MRI volumes were generated; the latter was used to extract interleaved sagittal and coronal cine-MRI centred in the tumour and as ground truth for validation purposes. Figure 1 shows the derived cine-MRI for each simulated patient. We will refer to the simulated patients as patients throughout the manuscript.

Table I. Range of motion difference [mm] and baseline difference [mm] between mean cycle and free-breathing signal over the selected temporal window for the six lung cancer patient motion traces included in this study.

<table>
<thead>
<tr>
<th>Mean cycle vs. Free-breathing signal</th>
<th>Range of motion difference [mm]</th>
<th>Baseline difference [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Chest AP 0.5</td>
<td>Diaphragm SI 2.2</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Chest AP 1.2</td>
<td>Diaphragm SI 4.4</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Chest AP 1.0</td>
<td>Diaphragm SI 2.3</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Chest AP 0.7</td>
<td>Diaphragm SI 6.5</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Chest AP 2.2</td>
<td>Diaphragm SI 9.3</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Chest AP 3.7</td>
<td>Diaphragm SI 2.3</td>
</tr>
</tbody>
</table>
2.2. Simulated MR acquisition parameters

The CT volumes were converted in MRI by means of a balanced Steady State Free Precession MRI sequence (i.e. TrueFISP) with the following parameters:

- repetition time (TR)/echo time (TE): 3.03ms/1.32ms
- flip angle: 45°
- accelerating factor: 2
- k-space subsampling: 65%
- signal-to-noise ratio (SNR): 20 dB
- acquisition matrix: 384×384×256 voxels
- volume resolution: 1×1×1mm³

From the converted in-room volumes, interleaved sagittal and coronal cine-MRI were centred in the tumour with an acquisition matrix of 384×256 pixels (frequency × phase encoding). The cine-MRI resolution was set to 1×1×3mm³ as reported by (Fast et al. 2017). Image acquisition time was ≈300ms per frame as generated by the XCAT phantom (Section 2.1).

2.3. Strategies to derive time-resolved 3DMRI

The five selected techniques to derive time-resolved volumetric MRI can be classified as fast/simplified strategies and global motion models. The selected fast strategies were:

- Propagation (Paganelli et al. 2018b) (PROP), which extends the displacement estimated between orthogonal cine-MRI and the corresponding slices extracted from a pre-treatment reference volume to estimate the entire in-room volume;
- Out-of-plane motion compensation (Seregni et al. 2017a) (OOPM), which corrects the in-plane motion by means of cine-MRI information and quantifies the out-of-plane motion using an a-priori information obtained during the planning phase.

The selected global motion models were:

- Fayad model (Fayad et al. 2012) (FAY), that correlates the motion estimated from pre-treatment imaging data to a surrogate extracted from a 2D image (i.e. cine-MRI);
- ROI-based model (Garau et al. 2019) (ROI), which revisits the Fayad model, proposing a solution based on regions of interest (ROIs);
- Stemkens model (Stemkens et al. 2016) (STEM), which relies on the maximization of a similarity metric that compares a coronal cine-MRI with the corresponding slice of a reference volume that is iteratively warped until convergence is reached.
The 2D and 3D deformable image registrations (DIR) required to implement the above-mentioned methods were performed through an optical flow algorithm (Zachiu et al. 2015). Additional details for each method are reported in the Appendix section.

2.4. Experimental design

The selected methods were tested in two simulated clinical scenarios: (i) application for tracking the 3D tumour position or (ii) application for motion estimation of the entire anatomy. As such, for the methods that required the definition of a specific surrogate (i.e. OOPM and FAY), the tumour motion was used for tumour tracking, whereas for the derivation of the whole anatomy, the diaphragm profile was extracted through a derivative filter and adopted as surrogate. For the other methods, a specific surrogate was not required, and motion signals were derived according to the specific approach (see Appendix section). The methods’ performance was evaluated using quantitative metrics (Section 2.4.1), patient-specific features (Section 2.4.2) and by calculating the required computational cost.

2.4.1. Quantitative evaluation

The performance of the methods in deriving time-resolved volumetric MRI was quantified by means of different evaluation metrics. Firstly, the tumour was segmented from the estimated and ground truth 3D MRI and compared in terms of tumour centroid distance (tCD), dice similarity coefficient (tDSC), Hausdorff distance (tHD) and mean contour distance (tMCD). Then, to estimate the methods’ performance on the entire volume, the root mean squared error (RMSE) between the grey-level values of the estimated and ground truth 3D MRI volumes was computed. Additionally, the ground truth 3D MRI volumes were registered on a reference volume (4D MRI exhale phase) (Zachiu et al. 2015). The obtained ground truth 3D vector fields were then compared with the 3D vector fields estimated by the methods by computing the mean absolute error in three different anatomical regions: diaphragm (dD), bones (bD) and heart (hD). Table II reports a summary of the acronyms used for the considered evaluation metrics.

<table>
<thead>
<tr>
<th>METRICS FOR QUANTITATIVE EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour</strong></td>
</tr>
<tr>
<td>tCD</td>
</tr>
<tr>
<td>tDSC</td>
</tr>
<tr>
<td>tHD</td>
</tr>
<tr>
<td>tMCD</td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
</tr>
<tr>
<td>RMSE</td>
</tr>
<tr>
<td>dD</td>
</tr>
<tr>
<td>bD</td>
</tr>
<tr>
<td>hD</td>
</tr>
</tbody>
</table>

A grouped patient analysis was performed in order to assess the methods’ performance over the entire patient population for each metric. A Friedman test (alpha=1%) was applied as statistical grouped analysis.

2.4.2. Patients classification

Patients were classified according to two indexes built upon intra-treatment tumour range of motion, intra-treatment diaphragm range of motion and breathing irregularity. The breathing irregularity was derived by computing the RMSE between each intra-treatment cycle and the average cycle, as reported in (Venkat et al. 2008), and finding the percentage of intra-treatment cycles with RMSE>2mm. Specifically,
\[ RMSE(i) = \sqrt{\frac{\sum_{i=1}^{n} (cycle_{\text{intra}}(i) - cycle_{\text{average}})^2}{n}} \]

\[
\% \text{irregularity} = \frac{n \text{ with } RMSE > 2 \text{ mm}}{n}
\]

where \( n \) is the number of breathing cycles, \( cycle_{\text{intra}}(i) \) is the \( i \)-th breathing cycle and \( cycle_{\text{average}} \) is the average breathing cycle.

As such, we derived two metrics describing pathological \( X_{\text{tum}} \) and anatomical \( X_{\text{anat}} \) patient characteristics:

\[
X_{\text{tum}} = \frac{Irr_n + Range\ Tum\ AP_n + Range\ Tum\ SL_n + Range\ Tum\ RL_n}{4}
\]

\[
X_{\text{anat}} = \frac{Irr_n + Range\ Diaph\ SL_n + Range\ Chest\ AP_n}{3}
\]

where \( Irr_n \) is the normalized percentage of breathing irregularity, \( Range\ Tum\ AP_n \), \( Range\ Tum\ SL_n \) and \( Range\ Tum\ RL_n \) are the normalized range of motion of the signals Tumour AP, Tumour SL and Tumour RL, while \( Range\ Diaph\ SL_n \) and \( Range\ Chest\ AP_n \) are the normalized range of motion of the signals Diaphragm SL and Chest AP.

Normalization was performed with ranges: 0-100 for \( Irr_n \), 2-30mm for \( Range\ Tum\ SL_n \), 1-20mm for \( Range\ Tum\ AP_n \), 1-10mm for \( Range\ Tum\ RL_n \), 5-40mm for \( Range\ Diaph\ SL_n \) and 3.5-30mm for \( Range\ Chest\ AP_n \). Ranges for tumour signal normalization were derived from (Keall et al. 2006) and for diaphragm-related signals from (Murphy and Dieterich 2006). As a result, \( X_{\text{tum}} \) and \( X_{\text{anat}} \) range from 0 to 1, with zero corresponding to regular and limited organ motion and 1 to highly irregular and large breathing motion.

Table III shows, for each patient, the percentage of breathing irregularity and the values of the parameters \( X_{\text{tum}} \) and \( X_{\text{anat}} \).

<table>
<thead>
<tr>
<th>Patient</th>
<th>% of breathing irregularity</th>
<th>( X_{\text{tum}} )</th>
<th>( X_{\text{anat}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>0.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

3. Results

3.1. Grouped patient analysis

The performance of each method was first compared in terms of 3D tumour tracking. In this case, OOPM compensation and Fayad model were implemented using the tumour motion as surrogate. A grouped patient analysis was performed for each metric used for quantitative assessment on tumour (Figure 2a). tCD for PROP (1.1±0.7mm) and ROI (1.3±0.9mm) resulted significantly different from FAY (1.7±1.2mm) and STEM (1.7±1.4mm). Slightly higher errors (1.4±1.2mm) were also observed for OOPM, although not significant differences were observed with respect to PROP and ROI. Similarly, tDSC and tMCD for Propagation, OOPM compensation and ROI-based model were significantly different from Fayad model and Stemkens model. In terms of tHD, there was not significant difference among the methods when evaluating all patients. Figure 2b
shows a qualitative representation of the overlap between the ground truth and the estimated volume for a respiratory sample in two cases.

Figure 2. Grouped patient analysis - error distribution in case of tumour tracking. (A) tCD, tDSC, tHD and tMCD computed for Propagation, OOPM compensation, Fayad model, ROI-based model and Stemkens model. Significance levels are defined as *** (p<0.01). (B) Qualitative representation of the estimated volume (green) overlapped with the ground truth (violet) for two patients.

The performance of each method was also compared in terms of motion estimation of the entire anatomy. In this case, OOPM compensation and Fayad model were implemented using the diaphragm surrogate. A grouped patient analysis was performed for each metric used for quantitative assessment on the entire anatomy, as reported in Figure 3 for the different metrics. Significant differences were mainly found for diaphragm (dD) and heart estimation (hD), as well as for tumour motion estimation (tCD, tDSC and tMCD). Specifically, optimal tCD median errors was obtained by PROP (1.1±0.7mm vs. 1.7±1.4mm derived for STEM). When considering other anatomical regions, dD was quantified accurately by ROI (1.4±1.6mm vs. 2.2±2.7mm of STEM); bD ranged from 0.8±1.8mm of OOPM to 1.4±1.4mm of PROP; whereas hD was 2.1±2.2mm for PROP with the highest error in FAY (3.9±3.7mm). The highest median RMSE was found for Fayad model (>20).
3.2. Patient classification

In terms of 3D tumour tracking, the performance of the methods was further investigated by evaluating their relationship with the index $X_{\text{tum}}$. Specifically, the mean tCD produced for each patient was plotted as a function of the index $X_{\text{tum}}$ and the functions, which best fit the experimental data, were determined (Figure 4). The mean tCD of all the methods highlighted a linear increase. The lines with the lowest and highest slope were the ones produced by PROP and STEM, respectively. Additionally, a grouped analysis was performed for patients with $X_{\text{tum}} < 0.3$ and no significant differences were found for any metric (supplementary material, Figure S1). In particular for PROP, the median of tCD, tDSC, tHD and tMCD were estimated to be around 1mm, 0.94, 2.3mm and 0.7mm, respectively. For patients with $X_{\text{tum}} > 0.3$, tCD, tDSC and tMCD for STEM and FAY (2.3±1.4/2.6±1.2mm for tCD in STEM/FAY) were significantly different (p < 0.01) compared...
to PROP, which presented the lowest errors (1.1±0.7mm for tCD). The threshold set at 0.3 was defined empirically as to guarantee a homogenous patients’ distribution.

As regards the estimation of the whole motion, methods performance was evaluated, by plotting the mean dD produced by all the methods as a function of the index $X_{anat}$ and by determining the functions that best fit the experimental data (Figure 5).

As shown in Figure 5, the mean dD for Propagation and ROI-based model increased linearly, while the mean dD of OOPM compensation, Fayad model and Stemkens model exhibited an exponential trend. A first threshold was established empirically ($X_{anat} = 0.6$) at the $X_{anat}$ value where the performance of OOPM compensation, Fayad model and Stemkens model deviate from the performance of PROP and ROI-based model (as well as to guarantee a homogenous patients’ distribution). In addition, a second threshold ($X_{anat} = 0.3$) was defined with the purpose of introducing a further classification between very regular patients with low range of motion ($X_{anat} < 0.3$) and quite regular patients with intermediate range of motion ($0.3 < X_{anat} < 0.6$).
The performance of the methods according to the evaluated quantitative metrics are reported in supplementary materials for patients with $0 < X_{\text{anat}} < 0.3$ (supplementary material, Figure S2), $0.3 < X_{\text{anat}} < 0.6$ (supplementary material, Figure S3) and $0.6 < X_{\text{anat}} < 1$ (supplementary material, Figure S4). In general, for patients with $0 < X_{\text{anat}} < 0.3$, equal performance was achieved on diaphragm and tumour, whereas higher errors were quantified for PROP in bD and for FAY in hD. In case of $0.3 < X_{\text{anat}} < 0.6$, higher errors in dD (>2.5mm) were quantified for FAY and STEM; FAY presented also errors >3mm in hD. Significant differences were observed on tumour metrics between PROP and FAY. When $0.6 < X_{\text{anat}} < 1$, PROP and ROI presented lower errors in dD (<4mm) and bD (<2.5mm) as well as in tCD (<2mm) than other methods.

### 3.3. Computational cost

For every method, we evaluated the computational cost using a 3.20 GHz Intel Core i7 processor with a 64 GB RAM. Table IV reports the executing times.

We calculated both the time for the 3D vector field (VF) estimation and the time for the entire framework, which includes also the generation of the 3D MRI volume. For Propagation, OOPM compensation, Fayad model and ROI-based model, the time for the entire framework was calculated as the sum between the time for 3DVF estimation, which is typical of the method, and the time for generating a 3D MRI volume, which is the same for all the methods ($\approx 64s$). For Stemkens model, instead, we only calculated the time needed for the entire framework, since the estimation of a 3DVF and the generation of a 3D MRI volume cannot be separated at every iteration. A limit of three iterations was defined in the iterative process.

<table>
<thead>
<tr>
<th>Method</th>
<th>Time for 3DVF estimation [s]</th>
<th>Time for entire framework [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propagation</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>OOPM compensation</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>Fayad model</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>ROI-based model</td>
<td>15</td>
<td>79</td>
</tr>
<tr>
<td>Stemkens model</td>
<td>7</td>
<td>200</td>
</tr>
</tbody>
</table>

### 4. Discussion

#### 4.1. Study motivation and phantom simulations

A recent study proposed by (Fast et al. 2017) compared different tracking methods applied on 2D cine-MRI data, using automatic tumour segmentation against ground truth manual delineation. To date however, no comparison among different approaches for the estimation of time-resolved 3D MRI data for MRI-guidance has been reported in the literature. This has been motivated by the lack of a ground truth on patient data due to MR limitations preventing the acquisition of a full real-time 3D volume. Recently the importance of phantoms as tools to validate strategies in which patient data lack of a ground truth information has been reviewed deeply (Kainz et al. 2019). We therefore believe that the use of a digital phantom animated with patient-specific signals represents the ideal solution to validate and benchmark methods to derive time-resolved 3DMRI data, as also recently proposed for 4DMRI sorting techniques (Paganelli et al. 2018a).

In this study, we simulated on a digital phantom the 4D average respiratory cycle and cine-MRI acquisitions, using data from real patient acquisitions. Specifically, for the in-room simulation, we selected a temporal window where we performed the derivation of time-resolved volumetric MRI. This time interval was chosen such as to guarantee the following conditions: (i) the presence of at least one respiratory cycle for every considered patient; (ii) a larger range of motion with respect to the 4D average cycle on which the methods are built/trained; (iii) the closeness of the starting sample to the exhale respiratory phase of the 4D cycle, in order to preserve the motion model construction from baseline variations and to avoid a subsequent model updating (Fasst et al. 2015). The latter assumption is justified by the need to mimic a possible clinical use of MRI-treatment units in which 4DMRI data are expected to be acquired on-board (i.e. close in time with 2D cine-MRI).
MRI acquisition). As shown in Table I, the range of motion of the selected window is different from the range of motion of the mean cycle, thus guaranteeing to test the model on samples which are not seen during the training. As concerns baseline, it can be observed that patient P6 presents an evident baseline difference, in terms of diaphragm, between the average and intra-treatment signals. For this irregularly breathing patient, it was difficult to find an intra-treatment volume free from baseline variations with respect to the exhale volume of the 4D mean cycle.

4.2. Performance of the investigated methods for time-resolved volumetric MRI

The analyses carried out in this study focused on the performance of the selected methods in a 3D tumour tracking scenario and in the 3D motion estimation of the entire anatomy. These were also complemented by the evaluation of the methods with respect to a patient motion classification identified by two indexes: \( X_{\text{tum}} \) and \( X_{\text{anat}} \).

Overall, the Propagation approach was the method with lowest errors for the scenario of 3D tumour tracking. This was also confirmed by the analysis performed on patient classification with the threshold set on \( X_{\text{tum}} \). As a matter of fact, as opposed to the other methods, PROP does not rely on a motion model built on the 4D average respiratory cycle, thus providing the capability to account for intra-treatment conditions that differ from treatment planning (see Table I). As regards the estimation of the global anatomy with the threshold set on \( X_{\text{anat}} \), the Propagation strategy performed worse than the other methods in terms of bones, for patients with \( 0 < X_{\text{anat}} < 0.3 \) and \( 0.3 < X_{\text{anat}} < 0.6 \). Indeed, the method assumes a correlation between the cine-MRI motion and the whole anatomy, thus neglecting that the motion of anatomical structures (such as bones) included in the cine-MRI can be different from the overall motion. However, the method performed accurately in tumour motion estimation for all the patient classes (tCD < 1 mm for \( 0 < X_{\text{anat}} < 0.3 \) and \( 0.3 < X_{\text{anat}} < 0.6 \) and tCD < 2 mm for \( 0.6 < X_{\text{anat}} < 1 \)), because the cine-MRI data were centred in the tumour itself. Good performance was also observed for diaphragm and heart, because the anatomical information was usually included in the cine-MRI.

The OOPM compensation showed errors below 2 mm in regular patients with low range of motion, i.e. patients with \( X_{\text{tum}} < 0.3 \), but it was not able to compensate for intra-treatment motion which significantly differed from the average motion description provided in treatment planning. This is due to the fact that the method is based on the simple application of an OOPM derived from the planning phase, but not adapted to the intra-treatment phase. This limitation is also confirmed by the analysis on the global anatomy, where the method fails to account accurately for motion in irregular patients with a large range of motion (\( 0.6 < X_{\text{anat}} < 1 \)). It should also be noticed that for OOPM (as well as for Fayad), a specific surrogate (tumour vs. diaphragm) was selected depending on the considered clinical scenario (3D tumour tracking vs. estimation of the whole anatomy), affecting the performance of the method differently. We expect that the method performance would be different also if the chest signal (i.e. derived from an external respiratory belt) was used as surrogate for the derivation of the whole anatomy instead of the diaphragm. In our analysis we decided to test the diaphragm signal only, since (i) it presented a larger motion with respect to the chest signal and (ii) it was expected to be more correlated to internal anatomical changes due to respiration. In this context therefore, the selection of a specific surrogate represents a limiting factor, suggesting that the method lacks in gathering different anatomical motion components.

The ROI-based model reported errors within 2.5 mm on patients with \( X_{\text{tum}} < 0.3 \), whereas for patients with \( X_{\text{tum}} > 0.3 \) it performed better than OOPM compensation but worse than Propagation. Indeed, as opposed to OOPM compensation, it exploits the intra-treatment motion which allows adapting the model to the current condition. However, since the motion model is still created from the 4D mean cycle, it is not able to compensate for intra-treatment conditions that are different from treatment planning, as opposed to the Propagation approach. As regards the entire anatomy, errors lower than OOPM, Fayad and Stemkens models were measured for all patients. In few cases, the method underperformed in estimating heart motion (errors
above 4mm). This could be potentially solved by defining a specific ROI for this anatomical site, in addition to the ROIs defined for tumour and diaphragm.

Generally, Fayad model and Stemkens model performed worse than all other methods in both 3D tumour tracking and 3D motion estimation of the entire anatomy. The worse performance of these approaches with respect to the ROI-based model could be attributed to the fact that (i) the motion components (RL, AP, SI) are not considered separately during the model generation and (ii) the surrogate used to update the model does not consider a regional adaptation. In the ROI-based model, the motion components were considered separately during planning, and subsequently multiplied by the corresponding RL, AP and SI surrogates over different regions of interest during treatment. Conversely, in Fayad model the motion components derived during planning are multiplied during treatment only by the surrogate yielding the highest motion (i.e., tumour or diaphragm), which is generally the SI surrogate. Similarly, in the Stemkens model the information is reduced to a single surrogate for model application. This assumes a fixed relationship between the motion of the surrogate itself and that of the entire anatomy over the three anatomical components, which could be a limit, especially for irregular and uncorrelated respiratory motion. Indeed, the Stemkens model provided good results on the entire anatomy only on patients with \( 0 < X_{anat} < 0.3 \), since these patients are the ones with the lowest difference between the mean cycle signal and the free-breathing signal over the selected temporal window. For this reason, the similarity function converges to the optimal solution within a reasonable number of iterations. Another issue of the Stemkens method is its limited capability in properly compensating for motion in the AP direction, since the similarity is computed between the coronal cine-MRI and the corresponding slice extracted from the warped reference volume (details in Appendix). The problem could be solved by fitting the model on the sagittal cine-MRI, which contains more motion information in the AP direction but less anatomical details. Alternatively, a combination of both cine-MRI images could be used, at the expense of the computational cost.

Finally, in terms of computational cost, fast/simplified strategies turned out to be more efficient than global motion models. Specifically, the global motion model characterized by the highest executing time was the Stemkens model, because, at every iteration, the method requires to generate a warped volume, which takes \( \approx 64 \text{ s} \) in our current implementation.

### 4.3. Suggestions for time-resolved volumetric MRI

From the proposed comparative analysis, we derived suggestions to select one of these methods for deriving time-resolved MRI volumes based on a priori knowledge of patient motion. By acquiring cine-MRI data of the patient and simulating different possible scenarios in an in-silico framework provided by the proposed phantom, one can define patient characteristics and select the best approach for time-resolved volumetric MRI. It should be noted that the proposed simulation framework would benefit from additional patient cases, thus potentially improving the fitting procedure and subsequently providing a better patient classification. Table V reports therefore preliminary suggestions based on the dataset used in this study. Overall, Propagation and ROI-based model presented lower errors with respect to other methods in both tumour tracking and estimation of the entire anatomy for most of the patients’ classes.

Table V. Suggestions for time-resolved volumetric MRI. A tick is reported to highlight the preferred strategy in the motion estimation of a specific anatomo-pathological structure in the scenario of 3D tumour tracking or whole anatomy derivation.

<table>
<thead>
<tr>
<th></th>
<th>Propagation</th>
<th>OOPM compensation</th>
<th>Fayad model</th>
<th>ROI-based model</th>
<th>Stemkens model</th>
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<td></td>
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<tr>
<td><strong>3D tumour tracking</strong></td>
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<tr>
<td>( X_{tum} &lt; 0.3 )</td>
<td>Tumour</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>( X_{tum} &gt; 0.3 )</td>
<td>Tumour</td>
<td>✓</td>
<td></td>
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<tr>
<td><strong>estimation of the entire anatomy</strong></td>
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<tr>
<td>Diaphragm</td>
<td>✓</td>
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</tbody>
</table>
5. Conclusions

In this work, we presented a comparison between five different strategies proposed in the literature to derive time-resolved volumetric MRI from 2D cine-MRI data. Our study simulates the acquisition of ideal pre-treatment 4D MRI and in-room orthogonal cine-MRI data centred in the tumour, by means of an MRI digital phantom, and aims at providing a reliable tool to test and compare strategies for 3D tumour tracking and motion estimation of the entire anatomy.

We put forward the potential of this platform for in-silico studies focusing on the comparison, development, and improvement of methods able to derive time-resolved 3D MRI, as well as for benchmark definition in MRI-guidance for clinical end-users.

Acknowledgement

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Appendix

Propagation

The Propagation approach is a reconstruction method that allows estimating a 3D volume from interleaved cine-MRI slices (Paganelli et al. 2018b). The method is implemented according to the following steps:

- a 2D DIR is performed between the sagittal/coronal slices of the exhale phase of a pre-treatment 4D MRI and the corresponding sagittal/coronal slices from the in-room 2D cine-MRI;
- the 2D sagittal and coronal motion fields components obtained through DIR are replicated to all the slices in the space (e.g. the AP motion component as detected on the sagittal slice is replicated to all the other sagittal slices), assuming a correlation between cine-MRI motion and the whole anatomy. Redundant quantitative information is available in the SI direction, as the orthogonal cine-MRI images provide a measurement of the SI component on both the sagittal and coronal plane. Therefore, the overall SI component of the estimated motion field is modulated by computing the mean of the motion field SI components. Finally, the estimated 3D motion field is applied to the pre-treatment 3D volume to obtain the current 3D volume.

Out-of-plane motion

Out-of-plane motion compensation is a method that allows to correct the in-plane motion and quantify the out-of-plane motion of a specific respiratory phase, using both an a-priori and intra-treatment information (Seregni et al. 2017a).

The a-priori estimation workflow is as follows:

- for each 4D MRI volume, the sagittal and coronal slices with the same orientation and position of the in-room cine-MRI are extracted;
- the in-plane \( IPM^B \) and out-of-plane motion \( OOPM^B \) on sagittal and coronal slices are estimated through 3D optical flow registration with respect to the reference volume (4D MRI exhale phase);
- the in-plane motion is estimated through 2D slice-to-slice optical flow registration \( IPM^D \);
- a respiratory phase-specific in-plane motion correction is calculated as \( C = IPM^3D - IPM^2D \);
- a mask of diaphragm and tumour is defined for the sagittal slices of each respiratory phase of the 4D MRI dataset.

The intra-treatment estimation-correction workflow is then implemented through the following steps:

- the sagittal and coronal cine-MRI slices are acquired;
- the respiratory phase \( \phi \) is calculated by extracting from the sagittal slices the diaphragm profile or the tumour mask, depending on the selected surrogate;
- each sagittal and coronal frame is registered on the corresponding slice extracted from the reference volume \( IPM^2D \);
- the phase-specific in-plane motion correction is calculated as \( IPM^C = IPM^2D + C \);
- the out-of-plane motion is estimated, as measured in the corresponding phase of the 4D MRI;
- the estimated in-plane and out-of-plane motion are applied to the reference volume in order to obtain the current 3D volume.

Fayad motion model

The Fayad model (Fayad et al. 2012) is a global motion model approach which relies on a pre-treatment 4D MRI dataset to build the model and an in-room 2D navigator as surrogate for model application.

During planning the model is created by means of principal component analysis (PCA), giving as input:

- 3D vector fields (3DVFs), one for each 4D MRI volume, registered on the reference volume (4D MRI exhale phase);
- surrogate data extracted from a 2D image and exploited to train the model in order to establish a correlation with 3D displacements.
To build the model, the deformation fields (displacement vectors) are placed in a vector:

\[ d_j = [u_{1,1,j}, u_{1,2,j}, u_{1,3,j}, ..., u_{m,i,j}, ..., u_{M,i,j}, s_{1,j}, s_{2,j}, s_{N,j}]^T \]

where, \( u_{m,i,j} \) is the \( t \)th component of displacement for the voxel \( m \) (with \( 0 < m \leq M \)) at time point \( j \) (\( 0 < j < J \)) where \( J \) is the number of deformation fields, \( i = 1,2,3 \) for the \( x, y, z \) displacement respectively, \( M \) is the total number of voxels, and \( s_{N,j} \) is the displacement of the \( n \)th surrogate at time point \( j \) (\( N \) is the total number of surrogates per deformation field).

Then a matrix \( D = [d_1, d_2, ..., d_j, ..., d_j] \) is constructed and principle component analysis (PCA) is applied to finally obtain a good approximation of each possible motion state \( d(t) \) at an arbitrary time point \( t \). Using the matrix notation, the latter can be expressed as

\[ d = WE \]

where \( E = [e_1, ..., e_k] \) consists of the first \( K \) eigenvectors and \( W = [w_1, w_2, ..., w_k] \) are corresponding weights. Given that \( d_j = [u, s]^T \), \( d \) can be split into two separate equations

\[ u = E_u W \quad \text{and} \quad s = E_s W \]

where, \( E_u \) and \( E_s \) are constructed from the upper \( 3M \) rows and lower \( N \) rows of \( E \), respectively.

Then for the application step, the deformation field at the instant \( t \) is derived as:

\[ u(t) = E_u E_s^{-1} s(t) = B s(t) \]

**ROI-based motion model**

The ROI-based model (Garau et al. 2019) is a global motion model that revisits the Fayad model (Fayad et al. 2012) proposing a solution based on ROIs (Region of Interests).

In this work, the framework was implemented according to the method proposed by (Garau et al. 2019), but changing the ROIs definition and separating the \( x \) (RL), \( y \) (AP) and \( z \) (SI) components during the model generation and application.

The planning phase is characterized by the following steps:

- 3DVFs are calculated between a specific phase of the mean cycle and a reference phase (4D MRI exhale phase) by means of 3D DIR registrations. The 3DVF is divided into two ROIs, one corresponding to the entire volume (ROI 1) and one containing only the tumour (ROI 2), so deriving, for each ROI, a set of nine 3DVFs.
- To derive internal motion signals, the sagittal and coronal slices, with the same orientation and position of the in-room cine-MRI, are extracted from each 4D MRI volume. A 2D DIR is then performed between the ten 2D images of each set (coronal and sagittal), considering the slices derived from the 3D reference volume as fixed images. Like for 3DVFs, a coherent division in ROIs is applied. 2DVFs (obtained by 2D DIR) are then masked by segmenting the anatomical structures of interest in each respiratory phase. Specifically, the 2DVF of ROI 1 is masked on the diaphragm, while the 2DVF of ROI 2 on the tumour. The maximum value of the 2DVF in each direction is extracted and combined with 3DVFs.

For a respiratory phase in a specific ROI, the 3DVF and maximum values of 2DVF are placed in a vector:

\[ d_{j,ROI} = [3Dv_{1,1,j}, 3Dv_{1,2,j}, 3Dv_{1,3,j}, ..., 3Dv_{m,i,j}, ..., 3Dv_{M,i,j}, \max 2Dv_{1,j}, \max 2Dv_{2,j}, \max 2Dv_{3,3,j}]_{ROI\text{planning}} \]

where, the \( 3Dv_{m,i,j} \) is the \( t \)th component of the 3DVF for the voxel \( m \) (with \( 0 < m \leq M \)) at the respiratory phase \( j \) (\( 0 < j < J \)) where \( J \) is the number of 3DVFs (\( J = 9 \)), \( i = 1,2,3 \) for the RL, AP, SI
displacement respectively, $M$ is the total number of voxels, and $\text{max}2Dvf_{1,j}, \text{max}2Dvf_{2,j}, \text{max}2Dvf_{3,j}$ are the maximum values of 2DVF along RL, AP and SI respectively.

Then a matrix $D_{ROI}$ is constructed as follows:

$$D_{ROI} = [d_{1,ROI}, d_{2,ROI}, \ldots, d_{j,ROI}, \ldots, d_{f,ROI}]$$

with dimension $(3M + 3) \times f$.

By applying PCA as in (Fayad et al. 2012) along the first principal component, the eigenvalues and eigenvectors $E$ of the covariance matrix $D_{ROI}^T D_{ROI}$ are computed, where $E$ is composed by the upper 3 $M$ rows ($E_{3Dvf_{ROI}}$) and the lower 3 rows ($E_{max2Dvf_{ROI}}$).

Given that $d_{j,ROI} = [3Dvf_{RL}, 3Dvf_{AP}, 3Dvf_{SI}, \text{max}2Dvf_{RL}, \text{max}2Dvf_{AP}, \text{max}2Dvf_{SI}]^T$, also $E_{3Dvf_{ROI}}$ and $E_{max2Dvf_{ROI}}$ can be defined respectively as $[E_{3Dvf_{RL}}, E_{3Dvf_{AP}}, E_{3Dvf_{SI}}]^T$ and $[E_{max2Dvf_{RL}}, E_{max2Dvf_{AP}}, E_{max2Dvf_{SI}}]^T$. This allow to derive the motion model $B_{ROI}$ for the three considered motion directions as follows:

$$B_{ROI} = [E_{3Dvf_{RL}} E_{\text{max}2Dvf_{RL}}, E_{3Dvf_{AP}} E_{\text{max}2Dvf_{AP}}, E_{3Dvf_{SI}} E_{\text{max}2Dvf_{SI}}]^T$$

$$= [B_{ROI,RL} \ B_{ROI,AP} \ B_{ROI,SI}]^T$$

The treatment phase is then characterized by the following steps:

- 2D DIR is performed between the in-room sagittal and coronal frames and the corresponding slices extracted from the reference volume. Diaphragm and tumour masks are then used to derive in-room surrogates. In this case, differently from the planning phase, the minimum value of the VF is extracted in addition to the maximum value, in order to compensate for baseline drifts consisting in a deeper exhale of the intra-treatment sample with respect to the reference exhale phase. To define when using the maximum or minimum value, in-room contours are compared with the one of the reference planning volume: if their position is above the one of the reference volume, the minimum is selected; on the contrary, the maximum is used as surrogate.

- Each $B_{ROI}$ is applied by multiplying the $B_{ROI,RL}$, $B_{ROI,AP}$, $B_{ROI,SI}$ components with the new RL, AP, SI motion extracted from the 2DVF corresponding area. Specifically, the new 3DVF for each ROI is derived as follows:
  - in case of in-beam maximum value of the 2DVF
    $$\text{new}3Dvf_{ROI} = [B_{ROI,RL} \text{max}2Dvf_{RL}, \text{max}2Dvf_{AP} \ B_{ROI,AP}, \text{max}2Dvf_{SI} \ B_{ROI,SI}] \text{ROI}_{in,room}$$
  - in case of in-beam minimum value of the 2DVF
    $$\text{new}3Dvf_{ROI} = [B_{ROI,RL} \text{min}2Dvf_{RL}, \text{min}2Dvf_{AP} \ B_{ROI,AP}, \text{min}2Dvf_{SI} \ B_{ROI,SI}] \text{ROI}_{in,room}$$

- The two estimated motion fields are then combined together by taking the motion field $\text{new}3Dvf_{ROI,1}$ referred to the entire volume and substituting, only in correspondence of the tumour region, the motion field $\text{new}3Dvf_{ROI,2}$.

**Stemkens motion model**

The Stemkens model (Stemkens et al. 2016) exploits a 4D MRI dataset and compare the in-room 2D cine-MRI with the correspondent slice of a warped reference volume by optimizing a similarity metric.

The framework is characterized by the following steps:

- DIR is performed on the 4D MRI volumes using a 3D optical flow algorithm with the exhale phase as a reference volume. This results in a set of 3DVF$s$, denoted as $VF_m (x, y, z)$ where $m$ is the respiratory phase and $x, y, z$ represent the spatial coordinates. A parameterized subject-specific motion model is then built from these 3DVF$s$. Similarily to Fayad et al. (Fayad et al. 2012), a matrix of concatenated motion vectors $X = [X_1 \ldots X_m]$ is formed in which:
\[ X_m = (VF_m^x(1,1,1), VF_m^y(1,1,1), VF_m^z(1,1,1), \ldots , \]
\[ VF_m^x(X,Y,Z), VF_m^y(X,Y,Z), VF_m^z(X,Y,Z))^T \]

\( X, Y \) and \( Z \) are the matrix sizes in \( x, y \), and \( z \) direction and \( VF_m^{x,y,z}(x,y,z) \) are 3D motion vectors. Next, the zero sample mean of the matrix \( X \) is calculated by subtracting the sample mean \( \mu \) from the vectors \( X_m \):

\[ \bar{X}_m = X_m - \mu \]

From this, the matrix \( B = \begin{bmatrix} \bar{X}_1 \ldots \bar{X}_m \end{bmatrix} \) is constructed. The matrix \( B \) is used to calculate the eigenvalues \( \lambda \) and eigenvectors through a singular value decomposition (SVD):

\[ B = U\Sigma V^{-1} \]

The matrix \( U \) consists of nine 3D eigenvectors for every voxel. Using a linear combination of these eigenvectors, the 3D spatial transformation \( \hat{p} \) for each voxel is calculated through a small set of weights \( w \):

\[ \hat{p} = \mu + Uw \]

The subject-specific respiratory model is linked to the in-room 2D cine-MRI slices by registering the reference 3D volume to the 2D data through a linear combination of the first two principal components. By warping the 3D reference volume, in such a way that it corresponds to the incoming coronal 2D slice, a vector of optimized weights \( w_{opt} \) is calculated:

\[ w_{opt} = \arg\max_w \text{Sim} (I_{2D}, I_{3D,w}) \]

\( I_{2D} \) corresponds to the coronal 2D slice and \( I_{3D,w} \) to the warped 3D reference volume. The image similarity \( \text{Sim} \) is calculated on the overlapping 2D anatomy in the coronal slice because, opposed to the sagittal slice, more anatomical information is available on the coronal slice. An image similarity index based on the image gradients is used:

\[ \text{Sim} (I_{2D}, I_{3D,w}) = \frac{\sum_{l=1}^{L} M_{2D,3D}(x,y) \cos(2\Delta \theta_{2D,3D}(x,y))}{\sum_{l=1}^{L} M_{2D,3D}(x,y)} \]

\( M_{2D,3D}(x,y) \) is the product of the image gradient magnitudes and \( \Delta \theta_{2D,3D}(x,y) \) the difference between the image gradient directions of the 2D coronal slice and the overlapping 2D anatomy in the warped 3D reference volume. \( L \) is the total number of voxels in the overlapping 2D anatomy.

A pattern search algorithm is used to maximize the similarity. When converged, a full 3DVF is calculated for each 2D acquisition by applying the optimized eigenvalues \( w_{opt} \) to the model.
References


