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Review Article

Organ Movement and Targeting during Non-Invasive Therapy and Surgery

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Abbreviations FUS: Focused Ultrasound; NIS: Non-Invasive Surgery; ABC: Active Breath Control; KF: Kalman Filter; NN: Neural Network

Abstract

One of the major challenges faced during non-invasive treatment and surgery of tumours or cancers in abdominal organs such as the liver, lungs or kidneys is the continuous movement due to physiological processes. This motion creates the need for comprehensive treatment planning in order to understand the target movement, compute the relative motion of the energy delivery system and compensate for the motion during image-guided robotic surgery. Without correct motion estimation, the target volume may suffer from inaccurate dosage delivery and/or adverse effects on the surrounding healthy tissue. A number of approaches have been proposed to deal with motion tracking. A succinct review of the methods used in the motion estimation and management of moving target volumes in the major abdominal organs, such as lungs, liver and kidney, are presented in this paper.

Introduction

Unconscious physiological functions induce repetitive movement of the body and organs, making it difficult to operate precisely on a patient during computer aided surgery. During Non-Invasive Surgery (NIS), such as radio-surgery or Focused Ultrasound Surgery (FUS), organ movements may lead to dose uncertainties in the treatment volume and/or adverse effects due to exposure of surrounding organs or tissues. For image guidance, the most prevalent imaging modalities include Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Ultrasound (US). These imaging modalities are also utilized to quantify the nature and maximal extent of these movements in real-time. However, once the motion dynamics are understood, the accurate prediction and compensation for that motion in real-time and implementation of control strategies to compute and deliver the dosage in the intended target is equally crucial to the success of the treatment, with robotic techniques becoming more important to allow the necessary real-time execution. In order to aid in the understanding of the outcomes, as well as pros and cons, of the body of work available in this domain, the work can be categorized in terms of motion detection and compensation methodologies or in terms of the real-time imaging modalities used for capturing guidance information on specific organs during treatment or surgery. The outcomes of these studies has been evaluated and classified based on the motion management methods used for target organ.

Subsequent sections of this paper are organized as follows: The studies on methodologies for motion detection and tracking are reviewed in section 2. A comparative discussion on motion compensation techniques proposed for various surgical interventions is given in section 3. Finally, recommendations for non-invasive surgery systems are provided in section 4.

Methodologies for Motion Detection and Tracking

Respiration has a major influence on the movement of the liver, kidney and pancreas. Bussels, et al. [1] studied the effect of respiration on upper abdominal organs based on 12 subjects using dynamic MRI. The movement induced by respiration observed in the craniocaudal direction was 24.4±16.4 mm for the liver, 23.7±15.9 mm for the pancreas, 16.9±6.7 mm for the left kidney and 16.1±7.9 mm for the right kidney. Similar values for renal motion (18.0± 6.0 mm) were reported by Balter, et al. [2] using CT. Respiration also induces movements of the different organs in the anterior-posterior and lateral directions. Liu, et al. [3] determined that lung tumor movement is majorly influenced by diaphragm motion, with the displacement of local lung tumors reside below 1.0 cm during a normal breathing except for small lesions located in the lower half of the lung. Miyatake, et al. [4] evaluated the heart wall motion using Doppler signals from cardiac tissue. The ventricular posterior wall excursion velocity was 2.0 ± 0.6 cm/s in normal subjects. Watanabe, et al. [5] observed the intrafractional gastric motion and interfractional stomach deformity using CT Images. The average intrafractional motions were –12.1, 2.4 and 4.6 mm for the Superior-Inferior (SI), Lateral (LAT), and Ventro-Dorsal (VD) direction. The average interfractional motions of the centre of the stomach were –4.1, 1.9 and 1.5 mm for the craniocaudal, lateral and anterior-posterior directions, respectively.

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Target volume motion can be tracked using three strategies mainly [6]:

- Real time motion tracking
- Motion suppression methods
- Respiratory gating

Real-time motion tracking methods

In this method, a target volume in liver is tracked continuously in real-time. Patients are able to breathe normally and there is no need for a target volume motion margin for the treatment [7]. In real-time liver motion tracking, the target volume requires to be identified accurately and robustly in real-time. D'Souza showed that implanting internal fiducial marking at the target volume can help improving the direct tracking.

Rohlfing, et al. [8] demonstrated an intensity-based non-rigid registration method that registers gated MR images of liver induced by respiration motion. Wunderink, et al. [9] devised a method for the reduction of respiratory liver tumour motion by implanting fiducial markers in the liver. Park, et al. [10] proposed a 3D motion estimation algorithm to construct the motion traces using 2D positional information at each angular projection using fiducial markers. Harris, et al. [11] investigated the use of 4D-Ultrasound (4DUS) to track liver motion using 4DUS phantom-based tracking. Marquet, et al. [12] presented the use of a multiple beam 4DUS tracking system to track the 3D respiratory-induced motion of a small region of tissue in the livers of anaesthetized pigs. They used fiducial markers to characterize the liver motion. Koizumi, et al. [13] have used an iterative Lucas-Kanade Pyramidal (LKP) approach for a Non-Invasive Ultrasound Theragnostics System to track and follow moving body targets [14,15]. Auboiroux, et al. [16] have also implemented the LKP approach on a dataset of respiratory-gated MR Acoustic Radiation Force Imaging (MR-ARFI).

de Koste, et al. [17] reported a high variation in extent of displacements for right and left kidneys using 4DCT at 2.5 – 20 mm for right and 2.5 – 30 mm for left kidney. In a similar study, Kim, et al. [18] reported mean displacements of 13.0 mm and 10.0 mm for right and left kidneys. They also compared the extent of movement in supine and prone positions and concluded that alteration from the supine to the prone position did not change the amount of intrafractional movements of kidneys. Early studies using ultrasound by Suramo, et al. [19] reported a displacement of 19 mm for the right kidney. In a pilot study on 20 healthy volunteers [20] reported average movements of 21.50 ± 2.30 mm (right) and 9.66 ± 3.80 mm (left) in the craniocaudal direction and reported increased displacement under coached respiration. In a subsequent and more elaborate study on 110 subjects [21] reported displacements of 24.54 ± 6.4 (right) and 17.06 ± 3.66 mm (left) in the craniocaudal direction. In this study they also quantified the effect of abnormalities such as cysts, Agiomyolypomas (AML) and Renal Cell Carcinomas (RCC) on kidney movement and reported reduced movement in affected kidneys ($p < 0.01$).

Most of these studies report higher movement for the right kidney than the left which could be due to the proximity of the liver. Studies also show that the kidney generally does not retrace its path during inhale and exhale cycles [20] and the extent of maximum hysteresis can be ~5mm.

Since there exists no ground truth indicating the actual organ displacement a direct comparison in terms of accuracy cannot be made between any of the studies mentioned. One of the reasons for the variation in measured displacement could be the difference in anatomical locations that were tracked. For example, Bussels, et al. [1] measure the two-dimensional displacement of the centre of gravity (deduced from the organ contours) while [20] measured the position of the upper pole of the kidney. However these measurements can be used for defining maximum extensions of the kidney which is useful in determining the treatment margins.

The major difficulty with real time tracking in FUS or radio therapeutic treatment is that structures like ribs can often appear in the treatment delivery path for the target volume in a moving internal organ. To address this issue, several motion suppression methods were introduced.

Motion suppression methods

In motion suppression methods, movement of the clinical target volume in the abdominal organs are controlled by breathe holding and voluntarily or forced shallow breathing. The liver movements can then be estimated by using a smaller margin for breathing motion [22]. These methods have proven to be successful in reducing target volume margins, particularly for patients with large diaphragmatic excursion. Active Breathing control (ABC) provides internal immobilization of internal organs affected by respiratory motion, such as the liver. This is achieved using moderate assisted breath-hold techniques at the patient's comfort level. Zhong, et al. [23] showed that ABC can effectively reduce liver motion with long time breath-holding at end-inhale. Nguyen, et al. [24] demonstrated that, based on a population-based respiratory liver motion model estimated from breath-hold CT data set of ten patients using a finite element model as a framework, average liver displacements are (absolute mean±SD) 0.12±0.10, 0.84±0.13 and 1.24±0.18 cm in the left-right, anterior-posterior, and craniocaudal directions, respectively. Davies, et al. [25] demonstrated that the motion of the liver is predominantly in the Superior-Inferior (SI) direction with an average displacement (± SD) (quiet respiration) of 10 ± 8 mm (range 5-17 mm), respectively.

In the self-held breath hold method, the treatment is performed during the breath hold interval while the patient holds his/her breathe voluntarily and performs reproducible patterns of breathe hold. During the breath hold the motion of the patient's internal anatomy should be at a minimum. Treatment is suspended if the level of breath hold falls outside the predetermined tolerance window [26].

Forced shallow breathing with abdominal compression is an approach in liver motion control that uses abdominal compression devices to control organ motion [27]. A typical compression device uses compression arches and plates attached to the treatment base over the abdomen of a patient. The pressure applied to the abdomen is controlled by adjusting the positions of arches and plates. The pressure reduces diaphragmatic movement and improves liver motion estimation [9]. Moerland, et al. [28] measured kidney movements of 2mm - 24 mm and 4 mm - 35 mm for left and right kidneys using MRI under normal breathing. Under forced respiration the displacements measured were significantly larger, ranging from 10 - 66 mm (left) and 10 - 86 mm (right).

However, the success of motion suppression methods are highly dependent on patient selection as these methods are applicable only with patients who are capable to reproduce shallow breathing or breath-holding at each treatment fraction [6]. One possible solution to overcome this limitation is to use respiratory gating methods.

Respiratory gating methods

Respiratory gating is a process for continuously tracking the movement of target volume during normal breathing. Treatment is only delivered when the target volume is exactly in the predefined range or margin of motion, and the treatment is turned off when the target volume moves outside of the margin [29]. Respiratory gating is more comfortable for the patient as they are not required to hold their breath, with the treatment machine switching on and off at pre-defined segments in the respiratory cycle. However, because treatment is only performed during a specific fragment of the respiratory cycle, the time required to conduct the same treatment compared to other suppression methods [29] is increased. Berbeco, et al. [30] used external markers to predict motion for real-time image guided radiotherapy. The challenge in this case is that the position of the marker and the target volume must be correlated and maintained throughout the treatment. The gating window is typically centred on end-exhalation as it is most stable. Hallman, et al. [31] demonstrated that, for the liver, a gating margin at the end-exhale with a 20% phase window decreases the motion span by a factor of 10.

Tracking with markers on respiratory gating

Liver motion tracking with respiratory gating can be performed with either external or internal markers. For instance, external infrared markers can be placed on the abdominal surface so that a spirometer can measure the effect of respiratory motion on the liver. Internal fiducial markers can be implanted in the target volume in the liver to deliver motion estimation with higher accuracy [32].

The use of external markers is more common compared to internal marker mainly because implanting internal fiducial markers is an invasive procedure. Liver motion tracking with gating and external markers requires [33]:

- Reproducible breathing patterns; and
- Accurate motion compensation of the temporal and spatial liver position tracked by the external markers

Maintaining regularity in natural breathing can be difficult for patients. Visual and audio coaching can help a patient to breathe in similar reproducible patterns [34]. Kitamura, et al. [35] demonstrated that gated respiration combined with both external and internal markers significantly improves the accuracy real time liver motion estimation based on fluoroscopic tracking of an implanted fiducial marker in the target volume.

Abhilash and Chauhan [36] developed a correlation model that finds a mapping between the movement of external skin markers placed on the abdominal access window and the internal movement of the targeted organ (kidney in this case). They fine-tune the estimate using Adaptive Neuro-Fuzzy Inference System (ANFIS), thereby achieving a nonlinear mapping. The correlation model was tested on ultrasound image sequences collected from 20 healthy volunteers with a resulting targeting accuracy of more than 94% (Table 1).

Previous studies quantifying movement of the target volume in liver (in mm) from various imaging modalities and methods are summarized in **Error! Reference source not found**. Furthermore, Table 2 shows the advantages and limitations of motion management methodologies.

The main approaches to accounting for organ movement during surgery are (1) defining a Planning Target Volume (PTV) that is larger than CTV (Clinical Target Volume) so as to account for the maximal extent of organ movement (2) using respiratory gating wherein the treatment is administered only during intervals when the position of the organ is inside predefined limits and (3) synchronous surgery where the applicator moves synchronously with the target organ so as to cancel the relative movement. A planning target volume can be defined based on existing statistical data of the maximal extents of movement. However, respiratory gating and synchronous surgery require a predictive model of the target organ movement. A method for incorporating respiration induced movement in dose calculation for liver treatment is described in Lujan, et al. [37]. In some non-invasive treatment techniques like Focused Ultrasound Surgery (FUS) real-time tracking of the target organ might not be feasible and hence correlation models that map the skin maker position to that of the target organ might be useful.

Methodologies for Motion Prediction and Compensation

As non-invasive tumour treatment modalities such as High-Intensity Focused Ultrasound (HIFU) or proton therapy become more accurate and available, precision in predicting target volume location has become an important issue for treatment delivery. In this study the following motion prediction methods are considered as standard among commonly used techniques

i. Linear Regression (LR)

ii. Kalman Filter (KF) based motion prediction

iii. Hidden Markov Model (HMM)

iv. Kernel Density Estimation (KDE) based predictor

v. Support Vector Regression (SVR)

vi. Population-based Statistical Motion Model

vii. Thin Plate Spline (TPS) model and Dual Fourier series

viii. Neural Network (NN) predictors

These methodologies are summarized below (for comparison see in Table 3).

Keall, et al. [38] proposed a Multileaf Collimator (MLC) tracking method where leaf positions were adjusted to continually align the dynamic MLC beam aperture to the target. The geometric precision for tracking patient motion was 0.6 to 1.1 mm and the response time of the system was 160 ± 2ms. However, this result was observed from a 3 patient dataset. Preiswerk, et al. [39] proposed a population-based statistical motion model based on a priori 3D exhalation breath-hold US scans of the liver and applied this model on a real-time 2D US and MRI dataset. This method showed an average spatial prediction accuracy of 2.4 mm. Richa, et al. [40] developed a motion prediction model for temporal and spatial deformation of heart surface by combining a visual tracking method based on Thin-Plate Splines and a temporal motion model based on a dual Fourier series.

Table 1: List of studies quantifying motion tracking using various modalities and methods.

Authors	**Year**	**Imaging modality**	**Body Part**	**Movement of the target volume(in mm)**			**Author comments**	**Motion management method**
				Craniocaudal	anteroposterior	left–right		
Park et al.	2012	CT	Liver	16.5±5.7	5.3±3.1	2.8±1.6	Results indicate that, in general, the liver motion is most dominant in the craniocaudal direction, followed by the anteroposterior direction, and the left–right direction.	Real time tracking
Bussels et al.	2003	Dynamic MRI	Liver	23.7±15.9			The movements of the different organs in the anterior-posterior and lateral directions were less pronounced which is important the planning of a conformal radiation treatment for pancreatic cancer.	
			Pancreas	24.4±16.4				
			Kidney	16.9±7.9				
Liu et al.	2007	CT	Lung				Lung tumor motion is primarily driven by diaphragm motion. The motion of locally advanced lung tumors is unlikely to exceed 1.0 cm during quiet normal breathing except for small lesions located in the lower half of the lung.	
Miyatake et al.	1995	Doppler imaging	Heart(ventricular wall)				These results indicate that their Doppler imaging method can accurately represent tissue velocity and can facilitate visual assessment of ventricular wall motion.	
Watanabe et al.	2007	X ray/CT	Stomach	22.7		9.9	They recommend regular verification of gastric movement and shape before and during RT to individualize treatment volume.	
Wunderink et al.	2008	Fluoroscopy	Liver	4.1		1.8	Abdominal compression effectively reduced liver tumor motion, yielding small and reproducible excursions in three dimensions.	Motion suppression
Nguyen et al.	2009	CT	Liver	12.4±1.8		1.2±1	The proposed method has potential applications in online assessment of motion at the time of treatment to improve image-guided radiotherapy and monitoring of intrafractional motion.	
Wagman et al.	2003	CT	Liver	5.1-12.8			Gating of radiotherapy for liver tumors enables safe margin reduction on tumor volume, which, in turn, may allow for dose escalation.	Respiratory gating
Kitamura et al.	2003	Fluoroscopy	Liver	9±5	5±3	4±4	Tumor location, cirrhosis, and history of surgery on the liver all had an impact on the intrafractional tumor motion of the liver in the trans axial direction. This finding should be helpful in determining the smallest possible margin in individual cases of radiotherapy for liver malignancy.	
Berbeco et al.	2005	Stereoscopic imaging	Lung				Treatment margins that account for motion should be individualized and daily imaging should be performed to ensure that the residual motion is not exceeding the planned motion on a given day.	
Hallman et al.	2012	CT	Liver	9.7±5			Proposed registration method can calculate the trajectories of abdominal organs based on centre of mass and bounding box motion metrics.	
			Pancreas	5±1				
Rohlfing et al.	2004	MRI	Liver	10-34			The computed organ motion model can potentially be used to determine an appropriate respiratory-gated radiotherapy window during which the position of the target is known within a specified excursion.	
Davies et al.	1993	US	Liver	10±8			Data shows that MRI motion artefact reduction techniques which assume that either organ displacement, velocity or acceleration are constant are only applicable during certain phases of the respiratory cycle.	

Table 2: Pros and cons of motion management methodologies.

Methods	Pros	Cons
Real time tracking	No need for BH for the patient No need for suppressed motion management	The target volume in a moving internal organ can be covered in the treatment delivery path by other structures like ribs.
Motion suppression	Improved accuracy in tracking target volume	Applicable only to the patients who are capable to reproduce shallow breathing at each treatment fraction.
Respiratory gating	Improved accuracy in tracking and target shooting	Because treatment is on performed during a specific fragment of the respiratory cycle, it requires longer time to conduct the same treatment compared to other suppression methods

Table 3: List of studies with different methods for motion prediction and compensation.

Authors	Year	Imaging modality	Test subject	Body part	Motion prediction method	Pros	Cons
Sharp et al	2004	CT	Human	Lung	Linear regression (LR)	Simple to implement and fast in execution	Can suffer from poor prediction if the signal noise is random.
					Kalman filter (KF)	The recursive structure in KF allows its real-time execution without storing observations or past estimates	Prediction is difficult if the amount of available data small.
					Neural network (NN) predictors	NN has been observed as one the most accurate prediction methods [44].	Neural network (NN) predictors are largely dependent on prior knowledge.
Kalet et al.	2010	fluoroscopy	Human	Lung	Hidden Markov Model (HMM)	Generally HMM prediction outperforms linear methods.	HMM sometimes models poorly anticipate state transitions at points with large motion in the breathing cycle
Dan Ruan	2010	real position management system (RPM)	Human	Chest wall	kernel density estimation-based (KDE) predictor	This method is predominantly efficient for longer prediction times up to a second.	KDE does not perform well in sliding window adaptive training [44]. KDE prediction was degraded at 0.2 s latency while effects of full 3D data processing using Principal Component Analysis (PCA).
Krauss et al.	2011	stereoscopic x-ray fluoroscopy	Human	Lung	Neural Network (NN) Support Vector Regression (SVR) Linear Regression (LR) Kernel Density Estimation	The NN outperformed the SVR, LR and KDE predictors by 4%, 9% and 24%, respectively	This work is comprehensive, but mainly limited by the number of evaluated patients.
Richa, Bó et al.	2011	stereo endoscopy	Human Porcine	Heart	Thin-Plate Spline (TPS) model and Dual Fourier series	Considerable improvements were observed in tracking and prediction of heart surface motion.	This method can struggle with abrupt motion
Preiswek et al.	2014	US MRI	Human	Liver	population-based statistical motion model	Tumour locations can be predicted within clinically acceptable margins	This method depends on a priori data

Kalet, et al. [41] used Hidden Markov Model (HMM) to predict the future sequences and new observables. Their time average HMM prediction outperforms linear methods for system latencies longer than 400 ms. A Kernel Density Estimation-Based (KDE) predictor was presented by Ruan [42]. This method is particularly efficient for longer prediction times up to a second.

- Linear Regression (LR) can suffer from poor prediction if the signal noise is random. For instance, in an image with poor contrast, bones can create ambiguity with the target volume. This makes it difficult to estimate the motion velocity from two points.
- Estimating the state transition matrix using Kalman filter becomes difficult if the amount of data is particularly small.

Sharp, et al. [43] performed a comparison study of Linear Regression (LR) predictors, Neural Network (NN) predictors and a Kalman filter. They found the following observations:

Krauss, et al. [44] compared the performance of motion prediction based on Linear Regression (LR), Neural Networks (NN), Kernel Density Estimation (KDE) and SVR for 12 patients. The comparison of these methods was based on sample frequency, prediction latency, model update frequency and dimension of the input signal. The authors concluded that the NN outperformed the SVR, LR and KDE predictors by 4%, 9% and 24%, respectively.

Conclusion

Target volume ablation in internal organs is difficult because organs often have compound multifaceted motion influenced by multiple factors such as respiration, cardiac motion and diaphragm elasticity. Great improvements have been made over the last two decades in target visualization, localization and motion management. This article provides a snapshot of the current status of methods in motion tracking for internal organs. Real-time tracking, motion

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suppression and respiratory gating are the most commonly used methodologies for target volume tracking. One limitation with real time tracking is that the target volume in a moving internal organ can be covered in the treatment delivery path by other anatomical structures such as the ribs bones. Several motion suppression methods were introduced to overcome this limitation. However, motion suppression methods are practically applicable only to the patients who are capable to reproduce shallow breathing at each treatment fraction. Therefore, respiratory gating methods can be used to alleviate this issue where treatment can be delivered when the target volume is in the predefined margin of motion cycle, and the treatment is turned off when the target volume moves outside of the margin.

A study on the use of prediction to compensate for system latencies in real-time image-guided treatment system has been presented. Common prediction methods and the challenges related to their implementation were discussed. It has been noticed that LR predicts poorly with random signal noise. HMM often fails to predict correctly if there is large and abrupt motion which commonly occurs in kidney and liver motion. KF based methods requires a large training set, however the recursive structure of a KF allows its real-time execution without storing observations or past estimates. The NN based prediction methods were commonly observed to be relatively more accurate and robust compared other techniques. A combination of NN and Kalman filter therefore can be recommended for motion prediction and compensation for non-invasive surgery systems.

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