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Prediction and Characterization
of Lung Tissue Motion during Quiet Respiration

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Biomedical Physics

by

Benjamin Michael White

2013
ABSTRACT OF THE DISSERTATION

Prediction and Characterization of Lung Tissue Motion during Quiet Respiration

by

Benjamin Michael White

Doctor of Philosophy in Biomedical Physics

University of California, Los Angeles, 2013

Professor Daniel Low, Chair

Purpose: The purpose of this dissertation is to quantitatively characterize and predict lung tissue motion with the goal of improving the local control of lung cancer. This is accomplished by producing a biomechanical model of lung tissue motion during quiet respiration. This dissertation proposes the development of algorithms and protocols for the analysis of motion information in 4DCT images.

Methods: A cohort of 50 patients was acquired with a 16-slice CT scanner. This data was used throughout the dissertation. Based on the law of volume conservation, a relationship between the tidal volume and the geometric expansion of the torso was devised and used to improve breathing motion studies. The breathing patterns of these patients were used to characterize breathing patterns based on the measured external surrogate information with the aim of improving the efficiency of linear accelerator gating windows. A characteristic breath was
defined as an average breath for use in generating patterns representative of realistic motion for breathing motion studies. A prospective gating algorithm was developed to allow the acquisition of user specified breathing phases with a relatively simple model to accurately predict respiratory phase occurrence in order to reduce the number of scans necessary to obtain sufficient data for breathing motion modeling. A new term to the breathing motion model to account for cardiac induced lung tissue motion was developed to improve the accuracy of the model.

Results: Breathing studies can be optimized by placing the surrogate device between the third and fourth lumbar vertebra. Three types of breathing patterns were observed in the patient cohort. The hysteresis component of lung tissue trajectories was shown to be between 8 – 18 % of the volume filling component of motion. A simple prediction algorithm was shown to be a significant improvement over commercially available software. An additional term was devised to account for cardiac-induced lung motion and was shown to be accurate.

Conclusion: This dissertation has demonstrated new quantitative methods to characterize lung tissue motion. Future work includes incorporating the work described in this dissertation into a new fast helical CT image acquisition protocol for breathing motion modeling.
The dissertation of Benjamin Michael White is approved.

Michael McNitt-Gray

Patrick Kupelian

Steve Jiang

Dan Ruan

Anand Santhanam

Daniel Low, Committee Chair

University of California, Los Angeles

2013
To Taria and Maddox who encouraged me to finish
and
To my parents, Michael and Linda, I owe everything
and
To the loving memory of Francis Likon
# Table of Contents

Chapter 1: Introduction ................................................................................................................................. 1  
Motivation .................................................................................................................................................. 1  
Background ............................................................................................................................................... 4  
Overview of the Dissertation .................................................................................................................. 14  

Chapter 2: Quantification of the thorax-to-abdomen breathing ratio for breathing motion modeling † .... 21  
Introduction ............................................................................................................................................. 23  
Methods .................................................................................................................................................. 25  
Results ..................................................................................................................................................... 27  
Discussion ............................................................................................................................................... 28  
Conclusion .............................................................................................................................................. 29  

Chapter 3: Physiologically Guided Approach to Characterizing Respiratory Motion ‡ .................. 36  
Introduction ............................................................................................................................................. 38  
Methods .................................................................................................................................................. 39  
Results ..................................................................................................................................................... 42  
Discussion ............................................................................................................................................... 44  
Conclusion .............................................................................................................................................. 46  

Chapter 4: Distribution of lung tissue hysteresis during free breathing † ........................................... 50  
Introduction ............................................................................................................................................. 52  
Methods .................................................................................................................................................. 54  
Results ..................................................................................................................................................... 60  
Discussion ............................................................................................................................................... 61  
Conclusions ............................................................................................................................................. 62  

Chapter 5: Investigation of a Breathing Surrogate Prediction Algorithm for Prospective Pulmonary Gating † .................................................................................................................. 71  
Introduction ............................................................................................................................................. 73  
Methods .................................................................................................................................................. 77  
Results ..................................................................................................................................................... 85  
Discussion ............................................................................................................................................... 87  
Conclusions ............................................................................................................................................. 88
List of Figures

Figure 1.1: 5th volume percentile reconstruction of a 4DCT displaying the anatomical regions of interest........................................................................................................................................17

Figure 1.2: Normal distributions for $\alpha$ in units of mm / l..............................................18

Figure 1.3: Normal distributions for $\beta$ in units of mm s / l..............................................19

Figure 1.4: Abnormal distributions of $\alpha$ and $\beta$. The units for $\alpha$ are mm / l and the units for $\beta$ are mm s / l......................................................................................................................................................20

Figure 2.1: An example of the linear relationship between the torso surface volume expansion and the tidal volume..................................................................................................................30

Figure 2.2: Extrapolation example at the neck (a) and the pelvis (b). Fit to the data shown in red and the added extrapolation to zero volume expansion shown in black...............................31

Figure 2.3: A typical example of $\eta(i)$ displayed with a 50th percentile tidal volume image displaying the variation of $\eta(i)$ in the craniocaudal direction. The sharp spike in $\eta(i)$ occurs at the bellows. The values of $\eta(i)$ were interpolated through the slices containing the bellows…..32

Figure 2.4: Distribution of $\Sigma \eta(i)$ for the thorax and abdominal regions for the whole body dataset and the thorax dataset (denoted with † subscript). The similarity between the thorax regions and the abdominal regions of both datasets is apparent................................................33

Figure 3.1: Volume-flow curves for 2 patients in the study. An example of a Type 1 (a) patient and a Type 2 (b) patient is shown with the color-bar denoting the percentage of time the patient spent in a given 25 ml and 25 ml/s volume and flow bin........................................................................................................................................47

Figure 3.2: Histograms displaying the free breathing variability metric ($\kappa$) for Type 1 (a) and Type 2 (b) patients........................................................................................................................................48
Figure 4.1: The tissue trajectory was calculated by the $\vec{\alpha}$ and $\vec{\beta}$ vectors scaled by $v$ and $f$ respectively, which was calculated from the characteristic breath, and the angle between $\vec{\alpha}$ and $\vec{\beta}$, $\vartheta$…………………………………………………………………………………………………………64

Figure 4.2: Histograms displaying the distribution of the tissue displacement (a) and the distribution of the elongation at increasing tissue motion intervals (b)……………………………………65

Figure 4.3: Histograms summarizing the average distribution of the tissue elongation for the left and right lung across lung cancer, non-lung cancer, and combined patient data sets……………66

Figure 4.4: Airflow vs. tidal volume relationships for the entire breathing session (blue curves) and the unique characteristic breath (red curve) for one patient imaged in two separate sessions (a,b) and two additional patients (c,d)………………………………………………………………………………67

Figure 4.5: Elongation maps of different patients with (a,b) and without (c,d) lung cancer. The elongation distribution varies smoothly in the non-lung cancer patients and displays regionally high elongation at the tumor sights in the lung cancer patients………………………………………68

Figure 5.1: Workflow of the prediction process…………………………………………………………90

Figure 5.2: Illustration of the nomenclature used in this work. This is the peak of a single inhalation. The solid and dotted curves indicate the measured and predicted breathing signals respectively……………………………………………………………………………………91

Figure 5.3: Results of an AIC test for a model development patient…………………………………92

Figure 5.4: Average prediction time error $e_t$ in seconds for peak inhalation (a) and peak exhalation (b) of the ARMA (2,5) prediction as a function of prediction step. Data are shown for the 44 evaluated patients………………………………………………………………………………93
Figure 5.5: Average $\eta$ with the 95% confidence window for 44 patients at increasing prediction time steps. The solid line curve represents maximum inhalation while the dashed line curve represents maximum exhalation.

Figure 5.6: Histograms of the 240 ms prediction error for peak inhalation and exhalation for the ARMA model and commercial algorithm for 35 patients. (a) Peak inhalation for the commercial algorithm. (b) Peak exhalation for the commercial algorithm. (c) Peak inhalation for the ARMA algorithm. (d) Peak exhalation for the ARMA algorithm.

Figure 5.7: An example of a patient data set showing the comparison of the commercial algorithm and the ARMA model predictions.

Figure 6.1: Coordinate system for the cardiac-induced lung motion model.

Figure 6.2: Figure 6.2a shows an overlay example of the reference cardiac frame image with a randomly selected cardiac frame. In Figure 6.2b, the randomly selected cardiac frame warped by the calculated deformation vectors overlaid with the reference cardiac frame is shown. The pixels in red highlight a discrepancy between the reference and randomly selected cardiac frames.

Figure 6.3: The uncompensated cardiac-induced lung tissue motion is shown for a SA view of the left lung (a) and right lung (b). The corresponding model residual error is shown for the left lung (c) and the right lung (d).

Figure 6.4: A sample distribution comparison between the uncompensated cardiac-induced lung tissue motion $|\vec{X}|$ and the model residual error $|\vec{X} - \vec{y}h|$ for the left lung (a) and the right lung (b) shown in Figure 6.3.

Figure 6.5: Cumulative histogram comparison between the cardiac-induced lung tissue motion and the model residual error for all voxels in the right (a) and left (b) lungs.
Figure 6.6: A typical example of $\|\tilde{y}\|$ for a SA view of the left lung. The color scale is in units of mm.................................................................119

Figure 6.7: $h$ curves for the right (a) and left (b) lungs for the 10 subjects......................120
List of Tables

Table 2.1: Summary of the results for patients imaged in the thorax and abdominal regions…34
Table 2.2: Summary of the results for patients imaged only in the thorax. The values reported for Ση(i) Abdomen† were estimated assuming Ση(i) Total = 1.11……………………………………35
Table 3.1: Summary of the statistics for non-lung cancer and cancer patients separated into Type 1 and Type 2 subsets. Note: Type 3 is not displayed……………………………………………49
Table 4.1: Summary of the 15th and 85th percentile lung tissue elongation for increasing tissue displacement in each lung sub-region…………………………………………………………….69
Table 4.2: Percentage of cases showing significant difference between the respective comparisons……………………………………………………………………………………70
Table 5.1: AIC, FPE, and percent fit results for three particular ARMA parameter combinations for the process outlined in Figure 5.1 and Equation 5.3…………………………………………97
Table 5.2: Number of patients with missed or falsely tagged breath cycles for both prediction models…………………………………………………………………………………………98
Table 6.1: Table of variables introduced in this chapter……………………………………………………………121
Table 6.2: Summary of the average absolute error and average relative error for increasing cardiac-induced lung motion envelopes…………………………………………………………122
Table 6.3: Summary of average cardiac-induced lung tissue motion and average model residual error for the right and left lungs over all subjects in this study………………………………123
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Chapter 1: Introduction

Motivation

Lung cancer has been the leading cause of cancer deaths in the United States and is anticipated to remain the leading cause of cancer death through 2040. In 2006, there were over 196,000 new cases diagnosed with an incidence rate of 83 per 100,000 people. If lung cancer is not treated it has the potential to be lethal. Even with treatment, the prognosis for patients with lung cancer has been poor. In 2006 there were 160,000 reported fatalities due to lung cancer.

Lung cancer primarily manifests in two histology types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). These two histological lung cancer types comprise over 98% of lung cancer cases in the United States. NSCLC commonly presents in three forms: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. SCLC commonly presents in squamous cell carcinoma and mixed cell carcinoma. In general, SCLC metastasizes faster than NSCLC. The ratio of NSCLC to SCLC occurrence is approximately 4:1.

Since the histology of lung cancer cannot be determined in vivo, a system of tumor evaluation metric that was independent of the tumor histology was developed. The TNM cancer staging system uses information from the primary tumor site, tumor size, number of tumors, lymph node involvement, cell type, and the presence of tumor metastasis. This information is weighed with knowledge of disease progression to provide a prognosis and to devise a treatment regimen.

While treatment practices for lung cancer primarily depend on the TNM cancer staging system, it is common to use surgical, radiotherapy, and chemotherapy techniques. Surgical procedures to remove lung cancer tumors include segment removal, lobectomy, and
pneumonectomy. These procedures remove the bulk of the tumor but cannot be employed if the cancer includes non-localized lymph nodes. Surgery is rarely used in SCLC cases since the cancer is usually spread to distant lymph nodes before it can be diagnosed. Chemotherapy alone has only been used in palliative care for patients with stage IV lung cancer. Chemotherapy is generally used as a treatment to relieve symptoms of lung cancer. Both surgical procedures and chemotherapy treatments are enhanced by the use of radiation therapy. Radiation therapy is used to control and reduce tumor size with ionizing and non-ionizing radiation. Radiation therapy has been reported to improve the long term survival of lung cancer patients. Currently, the best possible prognosis is available for individuals who can receive all three treatment modalities. The scope of this dissertation is to improve the performance of radiation therapy for lung cancer by modeling lung tissue motion during free breathing.

The standard of care for patients with lung cancer undergoing radiotherapy is intensity modulated radiation therapy (IMRT). IMRT is an advanced radiation treatment delivery process used to treat challenging geometries. It precisely delivers an accurate and highly conformal dose to the target region. A treatment plan is created based on a simulation CT. The tumor volume is defined by a physician and a margin is added to create the target region. A dose is prescribed to achieve local control of the tumor and a plan is optimized for each patient. Each segment of the IMRT plan is delivered with different intensity and geometry. An important assumption of IMRT treatment planning is that the target remains stationary. This is not the case for lung cancer tumors which move with each breath. Due to the length of IMRT treatments, a single breath hold is impossible and multiple breath holds would not provide a consistent geometry that is identical to the planning geometry. A method to account for breathing motion in IMRT has been to increase the treatment margin that is used for the treatment plan. ICRU Report 60
defines the stationary target as the clinical target volume (CTV). \[4-8\] When the target is moving, the maximum displacement of the CTV is enclosed in the internal target volume (ITV). \[4-8\] Finally an additional margin, known as the planning target volume (PTV), is added to the ITV to account for daily setup errors and is used for IMRT treatment planning. \[4-8\] The only method to reduce the amount of healthy tissue irradiated under this target volume definition is to provide a more accurate definition of the ITV; this will spare more healthy tissue, which will reduce radiation-induced side effects. One way to improve the definition of the ITV is to model the motion of tissue during respiration.

Uncompensated breathing motion causes incorrect positional and volume information that adversely affects radiation therapy during image acquisition, treatment planning, and treatment delivery. \[8-33\] The dose required to increase the length of time before local control failure has been proposed to be in excess of 70 Gy. \[34\] At this dose, the damage to healthy lung tissue from incorrect positional and volume information could be significant and may lead to debilitating side effects or death. Side effects can range in severity from fatigue to pneumonitis. Combined with involuntary and erratic respiration of patients, which leads to errors in tumor delineation and artifacts in the delivered radiation therapy dose distribution, local control of lung cancer is a major challenge in radiation oncology. A promising solution to compensate for breathing motion is to model the respiratory motion of lung tissue. Modeling the motion of internal lung tissue and correlating it to measurable external surrogates will further the understanding of respiratory motion. This allows treatment planners to predict the impact of breathing motion on the dose distribution and develop strategies for compensating that motion.

Respiratory motion causes image artifacts, dose delivery artifacts, and increased dose delivered to healthy tissue. In this manner respiratory motion affects the entire workflow of
radiation therapy. Four-dimensional computed tomography (4DCT) is the process for obtaining images used to determine tissue motion. One of the principal applications of 4DCT has been to provide breathing phase-gated image datasets for treatment planning. The images are typically acquired while the patient undergoes quiet or coached respiration. The image datasets are used to characterize the motion of the tumor and normal lung tissues due to breathing. A challenge in respiratory 4DCT is the lack of breathing amplitude and period reproducibility. This can lead to the acquisition of images that provide redundant motion information or are acquired during an irregular breath and subsequently do not provide the data necessary for breathing motion characterization. The response in these cases is to repeat the scans, increasing the dose to the patient. Established 4DCT imaging protocols deliver nontrivial radiation dose to the patient. For radiation therapy patients, this dose (typically 2-4 cGy) is well below other sources of radiation dose, so these additional procedures add little dose to their treatment regimen. However, if the breathing motion analyses are to be taken in non-radiation therapy patients (e.g. for the study of other pulmonary diseases), the CT dose is significant. Improvements in 4DCT image acquisition will ease the dose limitation, allowing scanning sessions to be performed for a greater patient population with greater accuracy.

**Background**

The human lung consists of two conical shaped structures that are connected by the junction of the right and left bronchus. The structures each consist of the apex (superior), base (inferior), and one or two fissures. The apex is rounded and extends to the clavicle. The base is concave and abuts the diaphragm. The fissures define the lobes of each lung. The right lung contains three lobes and the left lung contains two lobes. The right and left bronchus branches
Breathing is an essential, semi-voluntary function that delivers oxygen to the blood and removes carbon dioxide from the body. It is regulated by the need to maintain acceptable levels of carbon dioxide in arterial blood. Inhalation is caused by contraction of the diaphragm, which creates a pressure vacuum to inflate the lungs. Oxygen is drawn into the lungs while the ribcage and diaphragm expands in the anterior and inferior directions respectively. The oxygen is drawn into the alveoli and passed on into the blood. Exhalation is caused by the relaxation of the diaphragm; however it can also be a forced action. Lung tissue elasticity aids in the passive contraction of the lungs as it returns to a deflated state. A baseline residual volume exists at maximum exhalation to prevent the lung from collapsing.

**Breathing Motion Models**

The human lung consists of two conical shaped structures that are connected by the junction of the right and left bronchus. The structures each consist of the apex (superior), base (inferior), and one or two fissures. The apex is rounded and extends to the clavicle. The base is concave and abuts the diaphragm. The fissures define the lobes of each lung. The right lung contains three lobes and the left lung contains two lobes. The right and left bronchus branches into a complex tree in each lung and ends in alveoli, where gas exchange takes place. An example of lung anatomy from a 4DCT can be seen in Figure 1.1.

Breathing is an essential, semi-voluntary function that delivers oxygen to the blood and removes carbon dioxide from the body. It is regulated by the need to maintain acceptable levels of carbon dioxide in arterial blood. Inhalation is caused by contraction of the diaphragm, which
creates a pressure vacuum to inflate the lungs. Oxygen is drawn into the lungs while the ribcage and diaphragm expand in the anterior and inferior directions respectively. The oxygen is drawn into the alveoli and passed on into the blood. Exhalation is caused by the relaxation of the diaphragm, although it can also be a forced action. Lung tissue elasticity aids in the passive contraction of the lungs as it returns to a deflated state. A baseline residual volume exists at maximum exhalation to prevent the lung from collapsing.

**Breathing Motion Models**

In 1999, Lujan et al.\[^{[64]}\] proposed a breathing motion model to describe the nature of respiratory motion. Based on observation, the authors noted that the motion of the diaphragm was asymmetrically periodic, with more time spent at maximum exhalation, and the direction of the motion was primarily oriented in the superior-inferior direction. Accordingly, the model was a one-dimensional function that assumed a fixed period and motion amplitude. A model to describe this kind of tissue motion can be expressed as:\[^{[64]}\]

\[
\begin{equation}
    z(t) = z_0 - b \cos^{2n} \left( \frac{\pi t}{\tau} - \phi \right)
    \tag{1.1}
\end{equation}
\]

In Equation 1.1, \( z \) is the tissue position, \( z_0 \) is the tissue position at exhalation, \( b \) is the maximum motion displacement, \( z_0 - b \) is the inhalation position and \( n \) is a parameter to describe the shape of the function, \( \tau \) is the period, and \( \phi \) is the starting respiratory phase. A probability distribution function was defined to express the probability of a piece of tissue to be found at a distance (\( z \)) from a reference position (\( z_0 \)) defined at exhalation:\[^{[64]}\]

\[
\begin{equation}
    p_{om}(z) = \left\{ nb \pi \left( \frac{z_0 - z}{b} \right)^{2n-1} \times \left[ 1 - \left( \frac{z_0 - z}{b} \right)^{1/n} \right]^{1/2} \right\}^{-1}
    \text{ for } z_0 - b < z < z_0
    \tag{1.2}
\end{equation}
\]
Equation 1.2 satisfies the definition of a probability distribution function since its integral equals 1 over the defined interval. The assumptions used to define the cosine model are not realistic for lung tissue during quiet respiration due to the irreproducibility of respiratory volume and phase.

Motion of lung tissues has long been known to differ during inhalation and exhalation, resulting in elliptical motion patterns. In 2002, Seppenwoolde et al. [65] furthered the work of Lujan et al. [64] by introducing a breathing motion model that addressed hysteresis motion. Based on fluoroscopic observations of radio-opaque clips implanted in patient lungs, the authors observed lung tissue to move in ellipsoidal patterns during quiet respiration. The hysteresis was modeled by introducing a phase shift to Equation 1.1 in a direction that is orthogonal to the superior-inferior direction. Cardiac motion was removed from the analysis by taking a Fourier transform of the unfiltered fluoroscopic data and using a high pass filter to remove data that corresponded to the frequency of the heartbeat. They found the superior-inferior directional component of the breathing motion to be the dominant direction of lung tissue motion. However, the contribution of the lateral and anterior-posterior motion was not negligible. Over the course of radiation therapy treatment, a fairly consistent, average tumor trajectory can be calculated. Ten of twenty-one patients in this study had noticeable hysteresis with 20% of the patients having more than 1 mm of hysteresis motion. [65] 35% of patients displayed measurable cardiac motion. [65] The cardiac motion was reported to be primarily in the left-right direction and ranged between 1 mm and 4 mm. While the authors stated that they were not proposing a breathing motion model, they concluded that breathing motion could be modeled as a function of time. The even powered cosine functions were only capable of modeling the motion of ideal trajectories that arise for regular breathing patterns. It is important to note that the parameters of the cosine functions could not be predicted as a function of time.
5D Breathing Motion Model

The basic hypothesis for the 5D breathing motion model is that respiratory phase (time) based modeling approaches are fundamentally flawed when modeling lung tissue motion under the conditions of quiet respiration. This is due to the inability of the phase based models to handle the irregularity of breathing in time and space. To accurately predict breathing motion of lung tissues, Low et al. [66] developed a breathing motion model utilizing airflow and tidal volume as surrogates for breathing. The breathing motion model relates the position of internal tissues to the tidal volume and breathing rate (airflow) at the time the positions are being determined. The tidal volume models the motion component due to lung filling and is described as the lung geometry as though the patient were able to breathe infinitely slow. Low et al. [67] hypothesized that hysteresis motion is due to pressure imbalances within the lung created during the act of inhaling and exhaling, and that the spatial displacement caused by these imbalances could be related to the rate of breathing, or the airflow in and out of the mouth. To arrive at the breathing motion model, a few assumptions were made for quiet respiration. The pressure imbalances were assumed to be proportional to the vacuum developed to generate inspiration and the airflow. Hysteresis motion magnitude was assumed to be proportional to the airflow. The breathing motion model assumed that the motion component due to tidal volume fluctuations was independent of the motion component due to airflow variations. As a consequence of this assumption, hysteresis motion due to pressure imbalances occurs with the same magnitude regardless of the tidal volume, and the tidal volume lung expansion component at a specific point in time would not depend on the rate of breathing. The breathing motion model expresses the position of internal lung tissue $\bar{X}$ as a function of tidal volume ($\nu$) and air flow ($f$). [66]
\[
\ddot{X}(v, f; \dot{X}_0) = \ddot{X}_0 + \ddot{\alpha}(\dot{X}_0)v + \ddot{\beta}(\dot{X}_0)f
\]

(1.3)

where \( \ddot{X}_0 \) is the position of the lung tissue at zero tidal volume and zero air flow (exhalation), \( \ddot{\alpha}(\dot{X}_0) \) accounts for motion due to lung filling, and \( \ddot{\beta}(\dot{X}_0) \) describes the hysteresis motion component. While time is not explicitly expressed in the model, it is implicitly considered in the time dependence of the tidal volume and airflow. The coefficients \( \ddot{\alpha} \) and \( \ddot{\beta} \) are determined by measured tissue positions acquired with deformable image registration from the 4DCT image datasets.

Zhao et al. [68] characterized the lung tissue motion patterns predicted with the 5D breathing motion model. The goal was to provide a quantitative assessment and pattern of the \( \ddot{\alpha} \) and \( \ddot{\beta} \) coefficients. This was the first large patient cohort report of the 5D breathing motion model. The patient cohort consisted of lung cancer and non-lung cancer patients. The distribution of \( |\ddot{\alpha}| \) and \( |\ddot{\beta}| \) was shown to smoothly vary throughout the lung with higher magnitudes existing in the inferior- posterior and lateral portions of the lungs respectively. In agreement with previously published literature, \( \ddot{\alpha} \) was shown to be oriented primarily in the craniocaudal direction. The right and left lungs had distribution patterns with different magnitudes. Patients with lung cancer did not display a smooth variation of \( |\ddot{\alpha}| \) and \( |\ddot{\beta}| \). Figure 1.2 and Figure 1.3 display a non-lung cancer patient with a smoothly varying of \( |\ddot{\alpha}| \) and \( |\ddot{\beta}| \). Figure 1.4 displays an abnormal pattern of \( |\ddot{\alpha}| \) and \( |\ddot{\beta}| \) for a lung cancer patient. An error analysis of the discrepancy between measured tissue positions and the 5D breathing motion model predicted positions showed that 90% of lung tissue voxels had less than 2.1 mm discrepancy. The average error from the deformable image registration algorithm was reported
to be 1.3 mm based on comparing the deformation vectors from the deformable image registration algorithm and the positions of 100 manually tracked landmarks.

The accuracy of the 5D breathing motion model was investigated by Low et al [67] in 2011. This work was the first mathematical test to determine the accuracy of the 5D breathing motion model. With a constant airflow constraint, the relative local tissue density change as a function of tidal volume was derived from the continuity equation by applying the chain rule to account for the model’s dependence on \( v \) and \( f \) rather than time. The derived equation shown in Equation 1.4 was valid as either the limit of the density \( (\rho) \) or airflow went to 0. [67]

\[
\nabla \rho \cdot \alpha = -\frac{1}{\rho} \frac{\partial \rho}{\partial v} \tag{1.4}
\]

The divergence of \( \rho \alpha \) provided the mechanism for calculating lung tissue density changes. Based on Gauss’s Theorem, the integral of the divergence of \( \rho \alpha \) over the whole lung volume was equal to the surface integral of an element normal to the lung surface: [67]

\[
\int_V \nabla \rho \cdot \alpha dV = \oint S \rho \alpha \cdot d\vec{S} = \oint S \rho \left( \frac{X(v,f;\vec{x}_0) - \vec{x}_0 - \vec{\beta}(\vec{x}_0)f}{v} \right) \cdot d\vec{S} \tag{1.5}
\]

When the airflow equals 0, (end inhalation and end exhalation) Equation 1.5 becomes: [67]

\[
\oint \rho \alpha \cdot d\vec{S} = \frac{1}{v} \oint \rho (X(v,f;\vec{x}_0) - \vec{x}_0) \cdot d\vec{S} \tag{1.6}
\]

Physiologically, the surface integral was the displacement vector for the total lung volume change due to inhalation at end inhalation. The relationship between lung volume and tidal volume has been well established. [69-72] Therefore, from Gauss’s theorem we can express Equation 1.6 as: [67]

\[
\int_V \nabla \rho \cdot \alpha dV = 1.11 \tag{1.7}
\]

A similar approach was used to analyze \( \vec{\beta} \). Since \( \vec{\beta} \) described the hysteresis motion of lung tissue, the approach was expected to be negligible due to \( \vec{\alpha} \) describing lung volume filling
and the independence of $\tilde{a}$ and $\tilde{\beta}$. The same analysis would not result in a unit-less quantity, so a ratio between the surface integrals of $\tilde{\beta}$ and $\tilde{a}$ was used and multiplied by the ratio $f_{\text{max}}/v_{\text{max}}$. Applying Gauss’s law and Equation 1.7 reduced the term to: \[ R = \frac{\int_{V} \nabla \cdot \tilde{\alpha} \, dV}{1.11 \times \frac{v_{\text{max}}}{f_{\text{max}}}} \tag{1.8} \]

The analysis showed the average measured $\int_{V} \nabla \cdot \tilde{a} \, dV$ was $1.06 \pm 0.14$, which was in close agreement with the predicted value of 1.11. The average measured R was $0.017 \pm 0.027$ for all patients compared with the predicted value of 0. The close agreements between $\int_{V} \nabla \cdot \tilde{a} \, dV$ and R with the predicted values of 1.11 and 0 demonstrated the high accuracy of the 5D breathing motion model.

The relatively low discrepancy and high accuracy of the model permitted the development of a biomechanical interpretation of the 5D breathing motion model. \[ \text{The interpretation considered a voxel of lung tissue ranging from 1 to 3 mm}^3 \text{ to contain between 125 and 375 alveoli arranged in a hexagonal grid.} \] \[ \text{This tissue element provided enough statistical significance to external stimuli. Each alveolus in a voxel is subject to stress and strain during respiration. The stress acting on a single alveolus within a voxel was expressed as a chain stretching from the alveolus to the pleural interface. Equation 1.8 shows the stress on a single alveolus ($i$) from one of its abutting neighbors:} \]

\[ P_{i}^{alv} + P_{i+1}^{w} + T_{i+1} = P_{i+1}^{alv} + P_{i}^{w} + T_{i} \tag{1.9} \]

In Equation 1.9 $P^{alv}$ was the alveolar pressure, $P^{w}$ was the radial stress from the alveolar membrane surface tension, and $T$ was the resistance of the alveolar membrane against respiration. If a transient balance of stress exists, any alveolus in the sac will be exposed to the same pleural pressure $P_{pl}$ as shown in Equation 1.10. \[ \text{[73]} \]
\[ P_{pl} = P_{i}^{alt} - P_{i}^{w} - T_{i} \]  

(1.10)

For this study the alveolar wall response was considered to be sufficiently rapid to allow a balance of alveolar pressures for quiet respiration. Under this condition, the recoil stress was equal to the transpulmonary pressure that inflates the lung and this equilibrium was maintained despite a change in volume and flow.

To develop the concept of strain for the 5D breathing motion model, a combination of two components was used. Normal stress \( \bar{\sigma}_{n}(V, f) \) expressed expansion of the tissue and shear stress \( \bar{\tau}_{n}(f) \) expressed a force perpendicular to the normal stress. As the tissue (n) experiences an infinitesimal change in volume (V) and flow (f) it follows that the change in strain (x) can be expressed as: \[ \delta x_{n} = \frac{\bar{\sigma}_{n}(V+\delta V, f+\delta f, \bar{x}_{0}) - \bar{\sigma}_{n}(V, f, \bar{x}_{0})}{E(\bar{x}_{0})} + \frac{\bar{\tau}_{n}(f+\delta f, \bar{x}_{0}) - \bar{\tau}_{n}(f, \bar{x}_{0})}{G(\bar{x}_{0})} \]  

(1.11)

where \( E \) is the Young’s modulus, \( G \) is the shear modulus, and \( x_{0} \) is the tissue position at maximum exhalation. Similar to the 5D breathing motion model, time was implicit as the strain was not a function of time. Assuming \( \bar{\sigma}_{n}(V, f_0, \bar{x}_0) \) was differentiable with respect to the respiratory volume and the airflow, a Taylor expansion of Equation 1.11 for \( \bar{\sigma}_{n}(V, f_0, \bar{x}_0) \) at \( V=V_0 \) and \( f=f_0 \) and \( \bar{\tau}_{n}(f, \bar{x}_0) \) at \( f=f_0 \) was performed. While the Taylor expansion returned linear and nonlinear terms, it was hypothesized that the linear terms were dominant so the strain was expressed as a first order approximation of the motion in Equation 1.12: \[ \delta x_{n} = \frac{1}{E(\bar{x}_{0})} \left( \delta V \frac{\delta \bar{\sigma}_{n}(V_0, f_0, \bar{x}_0)}{\delta V} \bigg|_{V=V_0} + \delta f \frac{\delta \bar{\sigma}_{n}(V_0, f_0, \bar{x}_0)}{\delta f} \bigg|_{f=f_0} \right) + \frac{1}{G(\bar{x}_{0})} \left( \delta f \frac{\delta \bar{\tau}_{n}(f, \bar{x}_0)}{\delta f} \bigg|_{f=f_0} \right) \]  

(1.12)

An expression for the total strain on the tissue was expressed by integrating over all the infinitesimal changes in the strain. The total tissue displacement \( \Delta \bar{x}_{n} \) was the accumulation of the total strain for all tissue elements as shown in Equation 1.13: \[ \bar{X}_{n} = \sum \Delta \bar{x}_{n} \]  

(1.13)
\[ \Delta \vec{X}_n = \]
\[ \int_0^{\vec{x}_0} \int_0^V \frac{1}{E(\vec{x})} \frac{\partial \bar{\sigma}_n(V, f_0, \vec{x})}{\partial V} \left|_{V=V_0} \right. dV d\vec{x} + \int_0^{\vec{x}_0} \int_0^f \frac{1}{E(\vec{x})} \frac{\partial \bar{\sigma}_n(V_0, f, \vec{x})}{\partial f} \left|_{f=f_0} \right. df d\vec{x} + \]
\[ \int_0^{\vec{x}_0} \int_0^f \frac{1}{G(\vec{x})} \frac{\partial \bar{\tau}_n(f, \vec{x})}{\partial f} \left|_{f=f_0} \right. df d\vec{x} \]  
\[ (1.13) \]

In order to simplify Equation 1.13, three variables were introduced: \( \tilde{\alpha}(\vec{x}_0), \tilde{\beta}_1(\vec{x}_0), \tilde{\beta}_2(\vec{x}_0) \). The \( \tilde{\alpha}(\vec{x}_0) \) term was related to the normal stress and the volume. The \( \tilde{\beta}_1(\vec{x}_0) \) term was related to the normal stress and the airflow. The \( \tilde{\beta}_2(\vec{x}_0) \) term was related to the shear stress and the airflow. The variables were inherent properties of lung tissue so the displacement vector could be rewritten and reduced to the 5D breathing motion model as shown in Equation 1.14.\[73\]

\[ \Delta \vec{X}_n = \int_0^V \tilde{\alpha}(\vec{x}_0) dV + \int_0^f \tilde{\beta}_1(\vec{x}_0) df + \int_0^f \tilde{\beta}_2(\vec{x}_0) df = \tilde{\alpha}(\vec{x}_0) V + \tilde{\beta}(\vec{x}_0) f \]  
\[ (1.14) \]

Physiological interpretations and terminology for \( \tilde{\alpha}(\vec{x}_0) \) and \( \tilde{\beta}(\vec{x}_0) \) were consistent with the 5D breathing motion model presented in Equation 1.3. \( \tilde{\beta}(\vec{x}_0) \) consisted of two components, \( \tilde{\beta}_1 \) and \( \tilde{\beta}_2 \), which were parallel or anti-parallel to \( \tilde{\alpha} \) and perpendicular to \( \tilde{\alpha} \), respectively. This relationship comes from the interplay between the normal stress and the shear stress. This interplay has been previously investigated in biomedical literature. \[74-87\] The angular relationship should follow a bimodal distribution. To check the angles between these tissue specific vectors, Equations 1.15 was developed:\[73\]

\[ \cos(\vartheta) = \frac{\vec{\alpha} \cdot \vec{\beta}}{|\vec{\alpha}| |\vec{\beta}|} \]  
\[ (1.15) \]

Equation 1.15 denotes the interaction between the Young’s modulus and shear modulus. The angle \( \vartheta \) was a metric to characterize the elongation of breathing trajectories. In comparing the results of Equation 1.15 for the patient cohort, the distribution of \( \vartheta \) was found to be bimodal and closely agreed with the published literature.
The biomechanical model demonstrated that the 5D breathing motion model introduced by Low et al\textsuperscript{[66]} in 2005 was a first order approximation of the physical interpretations of the 5D model parameters $\tilde{\alpha}$ and $\tilde{\beta}$. It can be correctly shown through Equations 1.13 and 1.15 that a decrease in stress and alveolar pressure in conjunction with an increase in resistance drives lung inflation in the model as it was reported in literature. By showing an elastic lung tissue model subjected to driving forces and comparing it to the results of the 5D breathing motion model, the utility of the 5D breathing motion model was demonstrated.

**Overview of the Dissertation**

The overall hypothesis of this dissertation is that the local control of lung cancer can be significantly improved by producing a biomechanical model of lung tissue motion during free breathing. This dissertation proposes the development of algorithms and protocols for the analysis of motion information in 4DCT images, then validating them in comparison to existing data \textsuperscript{[44, 49, 50, 66-68, 73, 88-101]}. The goal of this dissertation is to continue the development of a novel breathing motion model first proposed by Low et al\textsuperscript{[66]} by implementing a prospective image acquisition protocol and compensating for cardiac induced lung tissue motion, which degrades positional and volumetric information in radiation therapy.

In this dissertation, characterization refers to methods to classify a patient within a cohort based on features derived from data collected from breathing motion surrogates and a 4DCT. This includes evaluating data such as the cross-sectional volume expansion at each slice per unit tidal volume and analyzing that for each anatomic region (Chapter 2) as well as observing distinct patterns demonstrated through volume-flow curves (Chapter 3). Chapter 4 will transition the dissertation from discussing characterization of lung tissue motion to discussing the prediction of lung tissue motion by introducing the use of a biomechanical model of lung tissue.
trajectories. In this dissertation, prediction refers to the use of predictive models such as the 5D breathing motion model and the autoregressive moving average model to predict lung tissue trajectories and respiratory phase respectively. Chapters 5 and 6 will propose these predictive algorithms for prospective imaging and will evaluate their effectiveness in modeling lung tissue motion. Each chapter will progress the dissertation in detail as follows.

Chapter 2 describes a methodology to quantitatively measure the thorax-to-abdomen breathing ratio from a 4DCT dataset for breathing motion modeling and breathing motion studies. The study utilizes the relationship in Equation 1.7 with the law of volume conservation.

Chapter 3 describes a method to characterize radiation therapy patient breathing patterns based on measured external surrogate information. Breathing motion is not regular in time or space, so methods for its characterization are needed to improve the efficiency of linear accelerator gating windows for IMRT treatments.

Chapter 4 characterizes and quantifies free breathing lung tissue motion distributions. The distribution and modeling of hysteresis directly affects the accuracy of motion-compensated treatment planning and delivery. This approach defined a characteristic breath as an average breath for use in generating patterns representative of realistic motion for breathing motion studies.

Chapter 5 proposes a prospective gating algorithm to allow the acquisition of user specified breathing phases. The goal of the study was to use a relatively simple model to accurately predict respiratory phase occurrence. Allowing the user to define image acquisition at a desired respiratory phase would reduce the number of scans necessary to obtain sufficient data for the 5D breathing motion model.
Chapter 6 proposes the addition of a new term to the 5D breathing motion model to account for cardiac induced lung tissue motion. Cardiac motion was not previously considered in the 5D breathing motion model, but it is hypothesized to have a significant impact on local lung tissue.

Chapter 7 summarizes the impact of this dissertation on the 5D breathing motion model and discusses future work that will continue the improvement of the 5D model and breathing motion modeling in general. Future work will include the incorporation of the work discussed in Chapters 5 and 6 into a new fast helical CT image acquisition protocol. The use of the characteristic breathing from Chapter 4 in breathing motion studies will be discussed. This chapter will discuss the implementation and use of the characterizing methods from Chapter 2 and 3 in clinical practice.
Figure 1.1: 5th volume percentile reconstruction of a 4DCT displaying the anatomical regions of interest.
Figure 1.2: Normal distributions for \( \alpha \) in units of mm / l.
Figure 1.3: Normal distributions for $\beta$ in units of mm s / l.
Figure 1.4: Abnormal distributions of $\alpha$ and $\beta$. The units for $\alpha$ are mm / l and the units for $\beta$ are mm s / l.
Chapter 2: Quantification of the thorax-to-abdomen breathing ratio for breathing motion modeling †

Abstract

Purpose: The purpose of this study was to develop a methodology to quantitatively measure the thorax-to-abdomen breathing ratio from a 4DCT dataset for breathing motion modeling and breathing motion studies.

Methods: The thorax-to-abdomen breathing ratio was quantified by measuring the rate of cross-sectional volume increase throughout the thorax and abdomen as a function of tidal volume. Twenty six 16-slice 4DCT patient data sets were acquired during quiet respiration using a protocol that acquired 25 ciné scans at each couch position. Fifteen data sets included data from the neck through the pelvis. Tidal volume, measured using a spirometer and abdominal pneumatic bellows, was used as breathing-cycle surrogates. The cross-sectional volume encompassed by the skin contour when compared for each CT slice against the tidal volume exhibited a nearly linear relationship. A robust iteratively reweighted least squares regression analysis was used to determine $\eta(i)$, defined as the amount of cross-sectional volume expansion at each slice $i$ per unit tidal volume. The sum $\Sigma \eta(i)$ throughout all slices was predicted to be the ratio of the geometric expansion of the lung and the tidal volume; 1.11. The Xiphoid process was selected as the boundary between the thorax and abdomen. The Xiphoid process slice was identified in a scan acquired at mid-inhalation. The imaging protocol had not originally been designed for purposes of measuring the thorax-to-abdomen breathing ratio so the scans did not extend to the anatomy with $\eta(i) = 0$. Extrapolation of $\eta(i)$ to $\eta(i) = 0$ was used to include the entire breathing volume. The thorax and abdomen regions were individually analyzed to determine the thorax-to-abdomen breathing ratios. There were 11 image datasets that had been
scanned only through the thorax. For these cases, the abdomen breathing component was equal to $1.11 - \sum \eta(i)$ where the sum was taken throughout the thorax.

**Results:** The average $\sum \eta(i)$ for thorax and abdomen image data sets was found to be $1.20\pm0.17$, close to the expected value of 1.11. The thorax-to-abdomen breathing ratio was $0.32\pm0.24$. The average $\sum \eta(i)$ was $0.26\pm0.14$ in the thorax and $0.93\pm0.22$ in the abdomen. In the scan datasets that encompassed only the thorax, the average $\sum \eta(i)$ was $0.21\pm0.11$.

**Conclusion:** A method to quantify the relationship between abdomen and thoracic breathing was developed and validated.
Introduction

In radiation therapy, tumor motion resulting from breathing remains an important challenge \cite{12, 15, 17, 22}. While methods have been developed to limit this motion, better understanding of the natural breathing cycle remains important. This study was designed to quantify the relative thorax versus the abdomen breathing-induced body expansion. Understanding the relative expansion of thorax and abdomen could be used to guide the design of external breathing surrogates as well as assess the potential for abdominal compression \cite{15, 19, 43, 48, 50, 102-104}.

During inhalation, the torso expands by a volume proportional to the tidal volume. Tidal volume is defined as is the volume of air displaced by the lungs during the act of quiet respiration. The relationship between the torso expansion and tidal volume has been a subject of interest in lung physiology. In 1965 Agostoni et al.\cite{105} measured the relationship between the thoracic circumference and the volume of the lung. They defined the thoracic circumference from the apex of the lung in the cranial direction and the level of the dome of the diaphragm in the caudal direction. In the discussion they highlighted the challenge of defining a boundary between the abdomen and thorax during respiration. If the subject intentionally breathed from the chest, the rib cage expansion changed the defined boundary location of the thorax and abdomen in this study. Grassino et al.\cite{106} suggested direct measurement of the anteroposterior diameter change of the thorax and abdomen was a valid alternative, provided that the variable length of the chest wall was taken into account. The diaphragm applies pressure to the respiratory system during respiration. This pressure influences the configuration of the chest wall which in turn increases the variability in which the boundary between the abdomen and the thorax is defined. Konno and Mead\cite{107}, in an earlier study of the volume displacement in the
thorax, claimed the chest wall distended during breathing. With this contribution and assuming the diaphragm contracted isometrically, Grassino et al\textsuperscript{[106]} developed a method of calculating the various chest wall configurations in relation to the diaphragmatic expansion state during respiration. In doing so they neglected the considerable effect rib cage expansion has on the abdomen where abdominal wall displacement occurs at a fixed diaphragmatic length. Fixed diaphragmatic length refers to controlled breathing where the rib cage expansion is greater than during quiet breathing. This is referred to as thoracic breathing in this manuscript. Mead and Loring\textsuperscript{[108]} analyzed the abdominal displacements caused by the rib cage and claimed the rib cage volume displacement accounted for a significant portion of the total lung volume change. These manuscripts provided a valuable insight into respiration mechanics, the displacement of organs during respiration, and the thorax and abdomen anatomic boundary. However they were unable to demonstrate and quantify volume conservation during respiration.

Gated radiation therapy uses breathing cycle surrogates to determine the breathing phase in real time\textsuperscript{[50, 90, 93-95, 97, 109]}. One such system is a cylindrical bellows that is wrapped around the abdomen. The bellows system does not have the ability to measure the tidal volume of the lung, but it has been used in conjunction with spirometry to quantitatively measure tidal volume. Werner et al\textsuperscript{[49]} developed a method to correlate the spirometry measured tidal volume to the bellows by the CT based air content. The air content was determined from analyzing the volume averaged Hounsfield units of pixels within the lungs. Based on the ideal gas law and the typical temperature and humidity values encountered in clinics, the ratio of internal air content to tidal volume change was calculated to be 1.11\textsuperscript{[97, 110]}. Given the relative incompressibility of the abdominal contents, we hypothesized that the ratio of geometric torso expansion to tidal volume in the torso was also 1.11.
The widespread implementation of linear accelerator gating using both thoracic and abdominal surrogates led to the question of how much surface expansion was being expressed in the thorax and abdomen for radiation therapy patients. This work examined the thorax to abdomen ratio of expansion, determining the amount of volume change in each region as a function of tidal volume.

Methods

Data Acquisition

This study used a total of 26 patient data sets acquired using a 16-slice CT scanner (Philips 16-slice Brilliance CT) under an IRB approved 4DCT protocol. The data set was divided into two subsets. The first subset contained 15 patients with images acquired from the chin through the pelvis and the second subset contained 11 patients with only thorax image data. The image acquisition protocol acquired 25 ciné CT scans at abutting couch positions using 40 mAs and 120 kVp. Image reconstruction was performed with a 512 by 512 voxel matrix, an in-plane field of view of 50 cm, and 1.5 mm thick slices. A contiguous set of simultaneously acquired 16 CT slices was termed a couch position and each couch position covered 24 mm in the craniocaudal direction. The scans used a 0.46 s gantry rotation, 360° reconstruction, and 0.32 s between each scan. The total duration to acquire the 25 scans in each couch position was 18.2 s. On average, 12 and 25 abutting couch positions were required to span the thorax and torso, respectively.

The tidal volume was determined by simultaneous measurement of a spirometer and an abdominal pneumatic bellows. The spirometer (Interface Associates, Aliso Viejo, CA, VMM 400) had a 1 ml resolution and sampling rate of 100 Hz. To account for known drift in the
spirometer signal, the abdominal pneumatic belt (Philips Medical Systems, Cleveland, OH), known as the bellows, was used as an independent metric. The relationship between the bellows and spirometer was found to be highly correlated by Werner et al.\textsuperscript{[49]} over a time period equal to the time to scan a single couch position. A linear drift correction was independently applied to the spirometer signal for each couch position and used to convert the bellows signal into tidal volume.

**Volume Expansion**

The volume of the body was measured by masking every scan. The mask discounted pixels beyond the exterior of the skin using a threshold method. The mask pixel volume increased as the tidal volume increased. The relationship between the two measurements was approximated as linear. A robust iteratively reweighted least squares regression analysis\textsuperscript{[111]} was used to determine the volume expansion at each slice $i$ per unit tidal volume, defined as $\eta(i)$. The volume expansion of each slice was summed to calculate the breathing ratio, essentially the rate of body volume increase throughout the thorax and abdomen as a function of tidal volume. The sum $\Sigma\eta(i)$ throughout all slices was predicted to be the ratio of the geometric expansion of the lung and the tidal volume: $1.11^{[97, 110]}$. The boundary between the thorax and abdomen was selected to be the Xiphoid process as imaged at or near the 50\textsuperscript{th} percentile tidal volume. The thorax and abdomen regions were individually analyzed to determine the thorax-to-abdomen breathing ratios. The thorax-to-abdomen breathing ratio was defined as the ratio of $\Sigma\eta(i)$ individually determined for the thorax and the abdomen.

**Extrapolation Correction**

Since the start and end craniocaudal positions of each CT scanning session had not been optimized to support this project, the first and last scans often had nonzero values of $\eta(i)$. To
allow a determination of $\Sigma \eta(i)$, the values of $\eta(i)$ were extrapolated until a slice position where $\eta(i) = 0$. The values of $\eta(i)$ decreased monotonically near the superior and inferior scan borders, and polynomials were evaluated to provide the extrapolation. To test the accuracy of the extrapolation, a patient with complete data was corrected with the extrapolation with the data at the beginning and end of the dataset artificially removed and the extrapolation compared with the actual values. A linear extrapolation was used for slices missing data at the neck and a second order polynomial extrapolation was used for slices missing data at the pelvis.

A large spike in the $\eta(i)$ was found in each patient at a location consistent with the bellows, which had been included in the mask. The presence of the spike was retrospectively corrected for by interpolating $\eta(i)$ for the slices that contained the bellows with a linear interpolation method. This process introduced $< 1\%$ uncertainty in $\Sigma \eta(i)$ for the slices under the bellows.

Results

An example of the robust iteratively reweighted least squares regression analysis\cite{111} used to determine $\eta(i)$ for a single slice is illustrated in Figure 2.1. The extrapolation correction at the neck and pelvis can be seen in Figure 2.2 for a single dataset. The extrapolation correction at the neck was done using a linear regression. The extrapolation correction at the pelvis required a second order polynomial fit. Figure 2.3 shows an example of the scaled $\eta(i)$ for each slice in the craniocaudal direction. These values are superimposed on the volumes of a mid-inhalation reconstructed scan.

The Xiphoid process was easily identifiable in the 50th percentile tidal volume scan. The $\Sigma \eta(i)$ results for the 15 patients with data in the thorax and abdomen are provided in Table 2.1.
The results are shown for slices superior to the Xiphoid process ($\Sigma \eta(i) \text{ Thorax}$), slices inferior to the Xiphoid process ($\Sigma \eta(i) \text{ Abdomen}$), all slices ($\Sigma \eta(i) \text{ Total}$), and the thorax-to-abdomen breathing ratio ($\Sigma \eta(i) \text{ Th} / \Sigma \eta(i) \text{ Ab}$). The average $\Sigma \eta(i) \text{ Total}$ for these patients was found to be $1.20 \pm 0.17$. The thorax-to-abdomen breathing ratio was $0.32 \pm 0.24$. The average $\Sigma \eta(i) \text{ Thorax}$ was $0.26 \pm 0.14$ and the average $\Sigma \eta(i) \text{ Abdomen}$ was $0.93 \pm 0.22$. Table 2.2 provides the results for the 11 patients imaged in only the thorax region. The results are shown in a similar manner as Table 2.1. Since these data sets did not have information for slices inferior to the Xiphoid process, $\Sigma \eta(i) \text{ Total}$ was assumed to be 1.11 so that $\Sigma \eta(i) \text{ Abdomen}$ was calculated by $\Sigma \eta(i) \text{ Total} - \Sigma \eta(i) \text{ Thorax}$. The average $\Sigma \eta(i) \text{ Thorax}$ for these patients was $0.21 \pm 0.11$. The average thorax-to-abdomen breathing ratio for these patients was $0.90 \pm 0.11$. The distribution of $\Sigma \eta(i)$ versus the 85th tidal volume percentile for the thorax and abdominal regions in both datasets can be seen in Figure 2.4. A Wilcoxon rank-sum test was used to test the statistical similarity of $\Sigma \eta(i)$ for the thorax and abdomen between the two datasets. $\Sigma \eta(i)$ for the thorax in patients that were imaged only in the thorax was statistically similar ($p=0.44$) to the thorax data of patients imaged from the neck through the pelvis. In the dataset that contained images from the neck through the pelvis, $\Sigma \eta(i)$ in the thorax was distinctly different ($p=3.4 \times 10^{-6}$) than the average volume expansion in the abdomen. For the patients imaged only in the thorax, the estimated abdominal volume expansion was statistically similar to the volume expansion of patients imaged in the abdomen ($p=0.66$).

**Discussion**

The majority of body expansion occurred in the abdomen. The thorax to abdomen breathing ratio showed the thorax component was only 32% of the abdominal component.
Therefore, placing a bellows on the abdominal region will typically provide greater sensitivity to respiratory motion than placing a bellows in the thorax region due to the greater body expansion in the abdomen. In this study the bellows was placed in the same anatomical location in the abdominal region for each patient scanning session. The slice with the greatest expansion occurred between the third and fourth lumbar vertebrae for the 15 patients with whole body scans. Placing the bellows at that location would provide the greatest body surface expansion per breath and, correspondingly, the best measurement precision.

The fundamental value of the total volume to tidal volume expansion of the body (1.11) served as a useful metric for evaluating thoracic CT images. The measured value for the total volume to tidal volume expansion of the body was found to be 1.20±0.17, which was only 7.2% higher than the expected ratio. This study measured the portion of this ratio in the thorax to be consistent between two groups, one with abdominal image data and one without.

**Conclusion**

A method to determine the relationship between abdomen and thoracic breathing was developed for breathing motion modeling and breathing motion studies. Two patient data sets containing CT information from the neck through the pelvis in one group and the thorax only in the second group were used in this study. The thorax and abdominal regions were statistically different in the first group while the thorax regions were statistically similar between both groups. These results suggested that the thorax to abdomen expansion ratio was a fundamental property that could be used for breathing motion modeling and breathing motion studies.
Figure 2.1: An example of the linear relationship between the torso surface volume expansion and the tidal volume.
Figure 2.2: Extrapolation example at the neck (a) and the pelvis (b). Fit to the data shown in red and the added extrapolation to zero volume expansion shown in black.
Figure 2.3: A typical example of $\eta(i)$ displayed with a $50^{\text{th}}$ percentile tidal volume image displaying the variation of $\eta(i)$ in the craniocaudal direction. The sharp spike in $\eta(i)$ occurs at the bellows. The values of $\eta(i)$ were interpolated through the slices containing the bellows.
Figure 2.4: Distribution of $\Sigma \eta(i)$ for the thorax and abdominal regions for the whole body dataset and the thorax dataset (denoted with † subscript). The similarity between the thorax regions and the abdominal regions of both datasets is apparent.
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<th>Ση(i) Abdomen</th>
<th>Ση(i) Total</th>
<th>Ση(i) Th. / Ση(i) Ab</th>
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*Table 2.1:* Summary of the results for patients imaged in the thorax and abdominal regions.
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<td><strong>Stdev</strong></td>
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† Estimated by assuming Ση(i) Total = 1.11

*Table 2.2:* Summary of the results for patients imaged only in the thorax. The values reported for Ση(i) Abdomen† were estimated assuming Ση(i) Total = 1.11.
Abstract

**Purpose:** To characterize radiation therapy patient breathing patterns based on measured external surrogate information.

**Methods:** Surrogate breathing data were collected during 4DCT from a cohort of 50 patients including 28 patients with lung cancer and 22 patients without lung cancer. A spirometer and an abdominal pneumatic bellows were used as breathing surrogates. The relationship between these measurements was assumed to be linear within a small phase difference. The signals were correlated and drift corrected using a previously published method to convert the signal into tidal volume. The airflow was calculated with a first order time derivative of the tidal volume for a window centered on the point of interest and with a window length equal to the CT gantry rotation period. The airflow was compared against the tidal volume to create ellipsoidal patterns that were binned into 25 ml x 25 ml/s bins to determine the relative amount of time spent in each bin. To calculate the variability of the maximum inhalation tidal volume within a free-breathing scan timeframe, a metric based on percentile volume ratios was defined. The free breathing variability metric (κ) was defined as the ratio between extreme inhalation tidal volumes (defined as >93% of the measured tidal volume) and normal inhalation tidal volume (defined as >80% of the measured tidal volume).

**Results:** There were 3 observed types of volume-flow curves, labeled Types 1, 2, and 3. Type 1 patients spent a greater duration of time during exhalation with $\kappa = 1.37 \pm 0.11$. Type 2 patients had equal time duration spent during inhalation and exhalation with $\kappa = 1.28 \pm 0.09$. The differences between the mean peak exhalation to peak inhalation tidal volume, breathing period,
and the 85th tidal volume percentile for Type 1 and Type 2 patients were statistically significant at the 2% significance level. The difference between κ and the 98th tidal volume percentile for Type 1 and Type 2 patients was found to be statistically significant at the 1% significance level. Three patients did not display a breathing stability curve that could be classified as Type 1 or Type 2 due to chaotic breathing patterns. These patients were classified as Type 3 patients.

**Conclusions:** Based on an observed pattern in volume-flow curves, a cohort of 50 patients was divided into three categories called Type 1, Type 2, and Type 3. There were statistically significant differences in breathing characteristics between Type 1 and Type 2 patients. The use of volume-flow curves to classify patients has been demonstrated as a physiological characterization metric that has the potential to optimize gating windows in radiation therapy.
**Introduction**

Human breathing patterns have been a topic of interest for a long time. Initial studies were conducted by Golla and Antonovich in 1929. They found that individuals had breathing patterns that were consistently regular or irregular. The possibility of classifying human respiratory motion was demonstrated. The first concept of stable individuality in breathing patterns was introduced by Dejours et al in 1961. Improvements in technology facilitated more quantitative studies of breathing patterns. Tobin et al conducted the first quantitative study of breathing patterns for healthy and diseased subjects using a spirometer mouth piece to measure the tidal volume. They noted a clear difference in breathing pattern between healthy and diseased subjects. They investigated the breathing characteristics of the patient cohort that included 65 healthy individuals (18 individuals over 60 years old), 22 asymptomatic smokers, 17 asymptomatic asthmatic patients, 15 symptomatic asthmatic patients, 28 chronic obstructive pulmonary disease patients, and 14 restrictive lung disease patients. The study found no significant difference in breathing period, tidal volume, and airflow among the healthy subjects subdivided by the subject’s sex or age. Smokers had increased tidal volume and decreased airflow compared to normal subjects. Asymptomatic asthmatic patients had no difference in the breathing characteristics compared to normal subjects. Symptomatic asthmatic patients had greatly increased tidal volume and airflow but a normal breathing period. Patients suffering from chronic obstructive pulmonary disease had increased breathing period, tidal volume, and airflow. Finally they found patients with restrictive pulmonary disease have increased breathing period and airflow while having a normal tidal volume compared to healthy subjects. These studies were not conducted for a radiotherapy patient cohort. A long term study conducted by Benchetrit et al demonstrated that the
breathing patterns of healthy subjects were reproducible for the same individual despite 4-5 years between study sessions. This led Benchetrit et al. [115] to conclude that despite an infinite combination of breathing variables, each individual had a single stable pattern that was consistent over a long period of time. [114] While breathing patterns exhibited a high degree of diversity, there was a resemblance between individuals [114] which could allow classifications into groups with similar characteristics.

This work investigates quiet respiration breathing patterns measured using two synchronized external surrogates to evaluate if the breathing patterns can be broadly characterized for radiotherapy patients. Characterization of breathing patterns and the observed breathing variability during a single treatment session may be useful in the optimization of respiratory gating methods.

Methods

Data Collection

Breathing data were collected from 50 radiotherapy patients; 28 lung cancer patients and 22 non-lung cancer patients while they were undergoing research 4DCT procedures. [49, 50, 66-68, 73] Patients were enrolled in this protocol under the criteria that each must have biopsy-proven or suspected cancer and must be prescribed radiation therapy with a prescription dose to the gross tumor volume of at least 45 Gy. Breathing tidal volume was measured using two simultaneously acquired breathing surrogates, a spirometer and a pneumatic bellows, gathered for more than 300 s. The spirometer was a commercial device (VMM400, Interface Associates) and consisted of a mouthpiece, tubing, and a small turbine connected to the system electronics. The spirometer
electronics provided an analog voltage signal proportional to airflow that was read by an ADC board (BNC 2110, National Instruments) with a 0.01 s sampling interval. Under constant airflow conditions, the system accuracy was within 3% as reported by Lu et al \[94\]. For breathing measurements, the spirometer had substantial drift artifacts that required the use of an additional breathing metric. To account for the spirometer signal drift, an air-tight cylindrical bellows shaped tube (76513NM10, Lafayette Instrument Co.) was wrapped around the abdomen; air pressure variation inside the bellows during respiration was measured by a built-in pressure transducer providing a voltage signal proportional to the air pressure. The same analog-to-digital converter that monitored the spirometer monitored the bellows voltage signal. \[49\] The quality of this data collection process has been discussed in detail in previous publications. \[49, 67, 68, 73\]

**Data Processing**

The spirometer-measured tidal volume exhibited a baseline drift and had a signal that if analyzed from sample to sample without additional processing would yield derivative measurements whose noise level would exceed the natural rate variation. \[49\] To remove the spirometer baseline drift, a piece-wise linear regression between the spirometer and bellows signals was independently calculated over 18.2 s sliding windows (the length of the sliding window was approximately equal to the 4DCT scanning duration at each couch position). The bellows signal drift correction and a small time offset (to model the time delay between abdominal motion and airflow) were determined by maximizing the correlation coefficient between the two signals for each 18.2 s time window. Werner et al \[49\] had used the same patient dataset for 4DCT analysis and determined that both signals were linearly related to the CT-based air content.
The tidal volume was smoothed using a 5th order polynomial over a time period corresponding to a single CT gantry rotation (0.46 s) and centered on the point where the airflow was being determined. A 5th order polynomial was selected because it provided the lowest order polynomial that maintained a good fit to the airflow result. The airflow was the time derivative of the smoothed tidal volume signal.

**Breathing Data Evaluation**

The goal of this study was to characterize respiration into categories that could be useful for treatment and treatment planning. Breathing variations were examined by plotting the airflow against the tidal volume to create volume-flow curves, representing individual breaths as elliptically shaped loops. The breathing cycle probability density distribution for an entire data collection session was created from the volume-flow curves and segmented into 25 ml and 25 ml/s volume and flow bins, respectively. The size of the bins was chosen to provide at most approximately 1% of the data points from an entire scanning session in each bin. These volume-flow curves were compared between patients to determine if any patterns emerged. The breathing traces of lung cancer and non-lung cancer patients were compared to determine if there were statistically significant differences between the two populations. The evaluated metrics were breathing period, peak-to-peak tidal volume, average maximum exhalation tidal volume, average maximum inhalation tidal volume, and average extreme inhalation tidal volume. Maximum exhalation and inhalation tidal volumes were defined at the 5th ($v_{05}$) and 85th tidal volume percentiles ($v_{85}$), respectively. The statistical significance of the differences between the listed metrics for the patients was assessed with a two-tailed Student T Test. Using tidal volume percentiles provided a consistent method of defining tidal volume extremes and the selected
values encompassed 80% of the respiratory signal. The extreme inhalation tidal volumes were
defined as volumes extending beyond the 98th tidal volume percentile, \( v_{98} \). To investigate the
variability within a free breathing scan timeframe, a metric based on percentile volume ratios
was defined. The free breathing variability metric (\( \kappa \)) was defined as the ratio,

\[
\kappa = \frac{v_{98} - v_5}{v_{85} - v_5}
\]

\( \kappa \) was developed to gauge the difference between extreme tidal volume inhalations (\( v_{98}-v_5 \)) and
normal tidal volume inhalations (\( v_{85}-v_5 \)). A two-tailed Z Test was performed to check the
statistical difference between Type 1 and Type 2 patients.

**Results**

The breathing probability distributions showed that they could be characterized by
whether the patient spent less than, equal or more time during inhalation than exhalation. Out of
50 patients, the volume-flow curves showed that none of the patients spent more time during
inhalation than exhalation, 34 of the patients spent more time during exhalation (termed Type 1),
and 13 patients spent roughly the same time during inhalation as exhalation (termed Type 2).
Volume-flow probability distributions for both observed types of respiratory patterns are shown
in Figure 3.1. The average values of \( \kappa \) for Type 1 and Type 2 patients were 1.37 ± 0.11 and 1.28
± 0.09, respectively. The mean tidal volumes for Type 1 and Type 2 patients were 602 ± 275 mL
and 409 ± 99 mL, respectively. The mean breathing periods were 4.9 ± 2.0 seconds per breath
and 3.5 ± 0.6 seconds per breath, for Type 1 and Type 2 patients, respectively. A two-tailed
Student Z Test found the mean tidal volume, breathing period, \( v_{98} \), and \( v_{85} \) to be statistically
different at the 5% significance level (p<0.05). The test did not find a statistically significant difference in the mean breathing amplitude, mean breathing period, and κ.

Among the 28 lung cancer patients, there were 21 Type 1 patients and 6 Type 2 patients. The average κ for those Type 1 and Type 2 patients were 1.39 ± 0.12 and 1.26 ± 0.07, respectively. The mean peak to peak amplitudes were 557 ± 257 mL and 442 ± 110 mL for Type 1 and Type 2 patients, respectively. The mean breathing periods for Type 1 and Type 2 patients were 4.5 ± 2.0 seconds per breath and 3.6 ± 0.6 seconds per breath, respectively. The lung cancer patients had an average κ of 1.36 ± 0.12, mean peak to peak amplitude of 520 ± 131 mL, and a mean breathing period of 4.30 ± 1.95 seconds per breath. The two tailed Student Z Test found no statistically significant difference between Type 1 and Type 2 patients with lung cancer.

Among the 22 non-lung cancer patients, there were 12 Type 1 patients and 8 Type 2 patients. The average κ for those Type 1 and Type 2 patients were 1.34 ± 0.08 and 1.30 ± 0.12, respectively. The mean peak to peak amplitudes were 676 ± 297 mL and 357 ± 54 mL for Type 1 and Type 2 patients, respectively. The mean breathing periods were 5.7 ± 1.9 seconds per breath and 3.3 ± 0.7 seconds per breath for Types 1 and 2 patients, respectively. The non-lung cancer patients had an average κ of 1.32 ± 0.09, mean peak to peak amplitude of 592 ± 268 mL, and a mean breathing period of 4.8 ± 1.8 seconds per breath. The two tailed Student Z Test found no statistically significant difference between Type 1 and Type 2 patients without lung cancer. A summary of the results can be seen in Table 3.1.
Out of the 50 patients, 3 displayed chaotic breathing tendencies. We termed these patients as Type 3 patients. Because of their wide respiration variability and a sample size of only 3 patients, no meaningful statistical analysis could be applied to the Type 3 patients.

**Discussion**

The difference between Type 1 and Type 2 patients was statistically significant at the 2% significance level for the mean peak exhalation to peak inhalation tidal volume \( (p=0.018) \), breathing period \( (p=0.014) \), and \( v_{85} \) \( (p=0.014) \). The difference between Type 1 and Type 2 patients was statistically significant at the 1% significance level for \( v_{98} \) \( (p=0.004) \) and \( \kappa \) \( (p=0.007) \). Observation of the volume-flow probability density provided an excellent metric to characterize individuals. Figure 3.1 displays the difference between Type 1 and Type 2 in terms of how long the patient spends in a given respiratory phase. Figure 3.1 shows the volume-flow curve for 2 patients in this study. Figure 3.1a shows a Type 1 breathing pattern and Figure 3.1b shows a Type 2 breathing pattern.

Type 1 patients constituted 68% of the patients in this study. Type 1 individuals breathed in a pattern that was consistent with quiet respiration; in other words, respiration was not forced. In this group, only 18% of the patients had Stage III or higher lung cancer. This was in contrast with Type 2 patients in which 88% of the lung cancer cases had Stage III or greater lung cancer. Type 2 patients displayed mild dyspnea with exertions that decreased the breathing period and maximum exhalation to maximum inhalation tidal volume. These exertions caused the saw-tooth breathing pattern observed with Type 2 patients. This pattern is not normal for humans. \[114, 115\] It is a taxing pattern that requires active exertions during both inhalation and exhalation.
The impact of using a spirometer as a respiratory surrogate has been discounted as the cause of the Type 2 pattern. Askanazi et al.\textsuperscript{[60]} reported on the effect a mouthpiece and nose piece has on respiratory measurements. They reported a 15.5\% increase in tidal volume and a 14.1\% increase in airflow. They concluded that the respiratory load could be impacted by either the use of the spirometer and nose piece or sensory stimuli between the face, mouth, and nose contributed to the increased values. Since the respiratory data acquired for this study was consistent, the difference between Type 1 and Type 2 patients could not arise from the surrogate but from the respiratory pattern of the individual. The Type 3 patients constituted only 6\% of the patients in this study. These patients displayed no discernible respiratory stability. The breathing traces were highly variable so the respiratory pattern was blurred with no single breathing phase displaying more stability. Published data has suggested patients with anxiety breathe with sporadic exertions at random respiratory phases, consistent with Type 3 patient breathing patterns\textsuperscript{[60, 114, 115, 127]}.

These results have important ramifications for phase-based breathing models. Phase based respiratory modeling assumes reproducibility in the breathing pattern. In addition to characterizing patients by breathing pattern type, $\kappa$ provided a metric to quantify the difference between extreme tidal volume inhalations and normal tidal volume inhalations. Due to the respiratory exertions driving the breathing patterns of Type 2 patients, $\kappa$ was smaller than Type 1 patients. This means there was approximately 10\% less variability in Type 2 patients at maximum inhalation than Type 1 patients. Figure 3.2 displays the distribution of $\kappa$ for Type 1 and Type 2 patients. This study provides a new metric that will aid in optimizing the efficiency of treatment gating windows used in clinical situations.
Conclusion

A cohort of 50 radiation therapy patients with and without lung cancer was analyzed to characterize the patients using breathing surrogate measurement. Based on observed breathing stability curve patterns, the cohort was divided into three categories called Type 1, Type 2, and Type 3. Type 1 patients exhibited a volume-flow probability density peak at exhalation. Type 2 patients had roughly equal probability density during both inhalation and exhalation. Type 3 patients exhibited highly variable and chaotic breathing patterns, but comprised only 6% of the cohort. The free breathing variability metric ($\kappa$) showed the ratio of extreme inhalation tidal volume and normal inhalation tidal volumes to be $1.37 \pm 0.11$ and $1.28 \pm 0.09$ for Types 1 and 2, respectively. The classification of patient breathing Type was shown to be novel and reliable characterization metric for optimizing the efficiency of gating windows during radiation therapy.
Figure 3.1: Volume-flow curves for 2 patients in the study. An example of a Type 1 (a) patient and a Type 2 (b) patient is shown with the color-bar denoting the percentage of time the patient spent in a given 25 ml and 25 ml/s volume and flow bin.
Figure 3.2: Histograms displaying the free breathing variability metric ($\kappa$) for Type 1 (a) and Type 2 (b) patients.
Table 3.1: Summary of the statistics for non-lung cancer and cancer patients separated into Type 1 and Type 2 subsets. Note: Type 3 patients are not displayed.
Chapter 4: Distribution of lung tissue hysteresis during free breathing

Abstract

Purpose: To characterize and quantify free breathing lung tissue motion distributions.

Methods: 47 patient data sets were acquired using a 4DCT protocol consisting of 25 ciné scans at abutting couch positions on a 16-slice scanner. The tidal volume of each scan was measured by simultaneously acquiring spirometry and an abdominal pneumatic bellows. The concept of a characteristic breath was developed to manage otherwise natural breathing pattern variations. The characteristic breath was found by first dividing the breathing traces into individual breaths, from maximum exhalation to maximum exhalation. A linear breathing drift model was assumed and the drift removed for each breath. Breaths that exceeded one standard deviation in period or amplitude were removed from further analysis. A characteristic breath was defined by normalizing each breath to a common amplitude, aligning the peak inhalation times for all of the breaths, and determining the average time at each tidal volume, keeping inhalation and exhalation separate. Breathing motion trajectories were computed using a previously published 5-dimensional lung tissue trajectory model which expresses the position of internal lung tissue, \( \tilde{X} \), as: 
\[
\tilde{X}(v, f : \tilde{X}_0) = \tilde{X}_0 + \tilde{\alpha}(\tilde{X}_0)v + \tilde{\beta}(\tilde{X}_0)f 
\]
where \( \tilde{X}_0 \) is the internal lung tissue position at zero tidal volume and zero airflow, the scalar values \( v \) and \( f \) are the measured tidal volume and airflow, respectively, and the vectors \( \tilde{\alpha} \) and \( \tilde{\beta} \) are fitted free parameters. In order to characterize the motion patterns, the trajectory elongations were examined throughout the subject’s lungs. Elongation was defined here by generating a rectangular bounding box with one side parallel to the \( \tilde{\alpha} \) vector and the box oriented in the plane defined by the \( \tilde{\alpha} \) and \( \tilde{\beta} \) motion vectors. Hysteresis motion was defined as the ratio of the box dimensions aligned orthogonal to and parallel to the \( \tilde{\alpha} \)
vector. The 15\text{th} and 85\text{th} percentile of the elongation were used to characterize tissue trajectory hysteresis.

**Results:** The 15\text{th} and 85\text{th} percentile bounding box elongations were 0.090±0.005 and 0.083±0.013 in the upper left lung and 0.187±0.037 and 0.203±0.053, in the lower left lung. The 15\text{th} and 85\text{th} percentiles for the upper right lung were 0.092±0.006 and 0.085±0.013, and 0.184±0.038, and 0.196±0.043 in the lower right lung. Both percentiles were calculated for tidal volume displacements between 5-15mm. In the left lung, the average elongations in the upper and lower lung were $\bar{\zeta} = 0.120 \pm 0.064$ and $\bar{\zeta} = 0.090 \pm 0.055$ respectively. The average elongations in the upper and lower right lung were $\bar{\zeta} = 0.107 \pm 0.060$ and $\bar{\zeta} = 0.082 \pm 0.048$ respectively. The elongation varied smoothly throughout the lungs.

**Conclusion:** The hysteresis motion was relatively small compared to the volume-filling motion, contributing between 8% and 20% of the overall motion. Statistically significant differences were observed in the range of hysteresis contribution for upper and lower lung regions. The characteristic breath process provided an excellent method for defining an average breath. The characteristic breath had continuous tidal volume and airflow characteristics when the breath was continuously repeated, useful for generating patterns representative of realistic motion for breathing motion studies.
Introduction

Low, et al [66] has hypothesized that breathing motion hysteresis is caused by the distribution of internal lung pressure imbalances during breathing. To arrive at their breathing motion model, a few assumptions were made for quiet respiration. The pressure imbalances were assumed to be proportional to the vacuum developed to generate inspiration and the vacuum was itself proportional to the airflow. Hysteresis motion magnitudes were assumed to be proportional to the airflow. The breathing motion model assumed that the motion component due to tidal volume fluctuations was independent of the motion component due to airflow variations. As a consequence of this assumption, hysteresis motion due to pressure imbalances would occur with the same magnitude regardless of whether the subject was near peak inhalation or exhalation. Similarly, the tidal volume lung expansion component at a specific point in time would not depend on the breathing rate.

In respiratory physiology, hysteresis is defined as the difference between the transpulmonary pressure of inhalation (increasing volume) and the pressure of exhalation (decreasing volume) [117]. Transpulmonary pressure is defined as the difference between the alveolar pressure and the pleural pressure within the lung, which is not equally distributed throughout the lung. Therefore hysteresis is not equivalent at every point. The heterogeneous distribution in the transpulmonary pressure was first proposed to be caused by the distension of internal air spaces by the elastic forces surrounding the tissue [128]. Based on an idealized phantom of lung parenchyma, they suggested that tissue in the lung uniformly expanded with volume. The phantom was an enlarged alveolar geometry consisting of a rigid frame enclosed with latex to form a membrane. Known volumes of air were introduced into the phantom and the resulting membrane displacement was observed. Lambert et al [129] expanded these findings to
non-idealized situations by developing a mathematical model of the parenchyma utilizing the pressure and volume as metrics to calculate tissue stress, which they called tissue elasticity. The tissue elasticity was subsequently shown to be uneven throughout the parenchyma \[^{130-132}\]. Attempts to model the imperfect elasticity of the lung were made with nonlinear models \[^{132-136}\] and stress force heterogeneity of parenchyma strips \[^{137-140}\].

Advances in radiation therapy imaging enabled Seppenwoolde et al \[^{65}\] to perform real time measurements of gold markers implanted in the lung. The trajectories of the gold markers were observed and the marker paths were modeled as even power cosine functions in time, one for each orthogonal direction. They described the phase difference between the two paths as the magnitude of hysteresis. While the authors stressed they were not proposing a respiratory model, they discussed the possibility of modeling respiration as a function of time. However, because of breathing pattern irregularities, time alone was insufficient to model lung tissue motion.

The transport of gas within the lung exhibits simultaneous diffusion and convection which Paiva \[^{141}\] proposed to be a function of tidal volume, airflow, and respiratory period. The solution was based on matter balance for an infinitesimally small volume. He claimed that inhomogeneous lung ventilation was most likely caused by the irregular dichotomy of the bronchial tree.

While these studies attempted to characterize and quantify lung tissue motion during free breathing, they fell short in achieving a comprehensive characterization metric. Construction of a comprehensive characterization metric would account for the large variability in period and amplitude during the observational period. We propose instead a method to create a single characteristic breath that maintains the underlying respiratory patterns of the subject during the observational period. With the characteristic breath we will construct characteristic trajectories
for each lung tissue voxel during the observational period that mirrors the breath to breath lung tissue trajectories. Our characterization metric will provide a quantitative tool to create realistic and repeatable patient specific breathing patterns that can be used, for example, to drive dynamic lung phantoms. We will employ the characteristic breath, along with the measured motion model parameters, to determine the relative amount of hysteresis in lung tissue motion patterns.

Methods

Data Acquisition

This study recruited 47 patients on an IRB approved clinical trial; each imaged using a 4DCT protocol conducted on a 16-slice CT scanner (Philips 16-slice Brilliance CT). The patient cohort contained 26 lung cancer patients and 21 non-lung cancer patients. The protocol called for 25 ciné scans at abutting couch positions to image the lungs, using 0.75 mm thick slices. Each couch position took 18.2 s to acquire all 25 scans. The images were reconstructed using a 512 by 512 voxel matrix and an in-plane field of view of 50 cm. The slice thickness was 1.5 mm. The duration of recorded breathing data collected for each scanning session was in excess of 300 s.

The tidal volume was simultaneously monitored using a spirometer and an abdominal pneumatic bellows. The spirometer (Interface Associates, Aliso Viejo, CA, VMM 400) was sampled at a rate of 100 Hz and with a 1 ml tidal volume resolution. To account for known spirometer instrumental signal drift [94, 97, 104], an abdominal pneumatic belt (Philips Medical Systems, Cleveland, OH), known as the bellows, was used as an independent metric. An illustration of the experimental set up can be viewed in Figure 4.1 of Lu et al [97]. A pressure transducer measured the pressure change inside the belt during inhalation and exhalation. The
relationship between the bellows and spirometer was found to be highly correlated by Werner et al.\textsuperscript{[49]} over a time period equal to the time to scan a single couch position; 18.2 s. A linear drift correction was independently applied to the spirometer signal for each segment and used to convert the bellows signal into tidal volume\textsuperscript{[49]}. 

Airflow was calculated from tidal volume with a first order time derivative. The tidal volume was smoothed using a moving 5\textsuperscript{th} order polynomial fit to reduce sampling noise. The polynomial order was selected based on observing no substantial improvement for using higher order polynomial fits. An analytical derivative of the tidal volume was calculated over a period of one gantry rotation centered on the point where the airflow was determined.

**Characteristic Breath**

In order to characterize the average motion of lung tissue during respiration, the concept of a characteristic breath was developed. The characteristic breath was calculated from the respiratory signal as measured by the bellows, the absolute breathing amplitude being unnecessary for the subsequent analysis. The signal was segmented into individual breaths from maximum exhalation to maximum exhalation. Each breath was normalized to maximum inhalation, shifted in time to align at maximum inhalation, and linearly corrected for physiologic drift such that the beginning and end tidal volumes were equal and zero. Breaths exceeding one standard deviation in period or amplitude from their respective means were removed from subsequent analysis. One standard deviation was selected to conservatively exclude breathing outliers from the definition of the characteristic breath. The breaths were further subdivided into inhale and exhale components. This process resulted in a set of superimposed normalized breaths coincident in both amplitude and time at peak inhalation, and having zero amplitude at exhalation. The characteristic breath was defined as the average of the breaths in time at each
tidal volume, separately determined during inhalation and exhalation. The airflow was calculated by a first-order time derivative of the characteristic breath. The characteristic breath provided the airflow and tidal volume samples that, along with the 5D breathing motion model, provided the hysteresis evaluation.

**5D Breathing Motion Model**

In 2005, Low et al.\[^{66}\] proposed a motion model that employed tidal volume and airflow as measurable surrogates for the breathing cycle. The breathing motion model described the position of internal lung tissue \( \mathbf{\tilde{X}} \) as a function of tidal volume \( v \) and air flow \( f \) for tissue positioned at \( \mathbf{\tilde{X}}_0 \) during tidal exhalation, \( v = f = 0 \)^\[^{66}\]

\[
\mathbf{\tilde{X}}(v, f : \mathbf{\tilde{X}}_0) = \mathbf{\tilde{X}}_0 + \alpha(\mathbf{\tilde{X}}_0)v + \beta(\mathbf{\tilde{X}}_0)f
\]

(4.1)

where \( \alpha(\mathbf{\tilde{X}}_0) \) accounted for motion due to lung filling, and \( \beta(\mathbf{\tilde{X}}_0) \) described the hysteresis motion component. While time was not explicitly expressed in the model, it was implicitly considered in the time dependence of the tidal volume and airflow. The coefficients \( \alpha \) and \( \beta \) were determined using measured tissue positions acquired by conducting deformable image registration on 4DCT images that were acquired with simultaneous quantitative spirometry. The model has been used to evaluate both tumor and normal lung tissue motion and initial indications show the model to be sensitive to radiation-induced tissue changes\[^{73}\].

The breathing motion model employed two vector fields, \( \alpha \) and \( \beta \), that, along with the breathing waveform, were used to describe the lung tissue motion during breathing. \( \alpha \) and \( \beta \), were not in and of themselves sufficient to provide a description of the motion. In order to visualize and analyze the complex nature of breathing motion, some simplification was required. In this work, we elected to define a characteristic breath as a breath that began and ended at the
same tidal volume (defined as 0 ml) with zero airflow. The breath had also to be truly characteristic of the patient’s breathing cycle and therefore the breath had to be derived from the patient’s breathing cycles. The second simplification was in the description of the breathing motion pattern. The characteristic breath allowed, along with $\alpha$ and $\beta$, the generation of a single, closed path for each tissue voxel.

**Image Registration**

Deformable image registration was used to map the motion of each tissue region. The image reconstructed at a tidal volume closest to end exhalation was employed as the reference scan. A fast normalized cross-correlation (NCC) method \[^{142}\] was used with a 11 by 11 by 10 pixel cube centered on each voxel, corresponding to a volume of 10.7 by 10.7 by 15 mm\(^3\). The center voxel was searched for in the bounded region for each scan. Each voxel in the non-reference image was searched for in the bounded region centered on the spatial location corresponding to the reference image. The bounded region was sufficiently large enough to contain the voxel in question. Image datasets were reconstructed with percentile tidal volumes corresponding to the percentage of time the surrogate measured a particular volume. Each breath has different inhalation and exhalation volumes. Exhalation (i.e. zero volume) was defined as the 5\(^{th}\) percentile, $v_5$, meaning the tidal volume was less than this value 5% of the time during the scanning session. Inhalation was defined as the 85\(^{th}\) percentile tidal volume; $v_{85}$. The reference image was chosen to be the scans closest to exhalation. The total tidal volume difference between successive scans was less than 100 ml, which corresponded to less than 8 mm of tissue motion. The search was first conducted with the scan nearest to tidal exhalation. Once the vector deformation map between that scan and the reference was determined, the next scan was selected. Rather than start the search assuming that the third scan had the same deformation as
the second, the second was extrapolated by the ratio of tidal volumes to provide the initial search space for the third scan. This process was repeated separately for the scans acquired during inhalation and scans acquired during exhalation.

Once the registrations were completed, the 5D breathing motion model was fit to the motion data using a Nelder-Mead Optimization Algorithm \cite{143} where the root mean least square distance between the measurements and the fitting of the breathing motion model was defined as \cite{73}:

$$\min_{\mathbf{X}_0, \mathbf{a}, \mathbf{\beta} \in \mathbb{R}^3} \sum_{i=1}^{25} \| \mathbf{\tilde{X}}_i - \mathbf{\tilde{X}}_0 - \mathbf{\tilde{a}} v_i - \mathbf{\tilde{\beta}} f_i \|$$

(4.2)

where $\mathbf{\tilde{X}}_i$, $v_i$, and $f_i$ were the tissue position, tidal volume, and airflow for the $i^{th}$ scan. The $\mathbf{\tilde{X}}_0$, $\mathbf{\tilde{a}}$, and $\mathbf{\tilde{\beta}}$ vectors in space $\mathbb{R}^3$ were the fitting parameters. The angle $\vartheta$ between $\mathbf{\tilde{a}}$ and $\mathbf{\tilde{\beta}}$ was determined with the expression:

$$\vartheta = \arccos \left( \frac{\mathbf{\tilde{a}} \cdot \mathbf{\tilde{\beta}}}{|\mathbf{\tilde{a}}||\mathbf{\tilde{\beta}}|} \right)$$

(4.3)

Lung Tissue Elongation

The phase difference between the volume and flow allowed the 5D breathing motion model to describe the complex lung tissue motion paths, but made a straightforward description of those paths challenging. Given the inherent complexity of the trajectories, we elected to describe the hysteresis behavior by building a bounding box around the closed trajectory, with one edge of the box parallel to $\mathbf{\tilde{a}}$ (termed the parallel side), the box lying in the plane of the $\mathbf{\tilde{a}}$ and $\mathbf{\tilde{\beta}}$ vectors, and whose width and length just encompassed the trajectory. The ratio of perpendicular to parallel box dimensions were defined as the tissue trajectory elongation $\zeta$. An illustration of the elongation geometry and terms can be seen in Figure 4.1. For example, when $\mathbf{\tilde{a}}$ and $\mathbf{\tilde{\beta}}$ were orthogonal, the elongation was:
\[ \zeta = \frac{\text{Max}(\beta f) - \text{Min}(\beta f)}{\text{Max}(\alpha v)} \]  \hspace{1cm} (4.4)

**Lung Subdivision**

Breathing motion magnitudes and characteristics are known to be functions of the location within the lungs. Most lung tissue motion has been shown to be oriented in the superior-inferior direction and the magnitude of the motion is greater in the inferior lung \[^{[65]}\]. The contribution of hysteresis is also expected to differ as a function of the position within the lungs. The apex of the lung should display an increased elongation as the motion in the superior-inferior direction is constrained. Furthermore the presence of varying types of tissue, such as a localized tumor, should have an effect on the relative contribution of hysteresis to the trajectory of the tissue.

Differences also exist between the right and the left lungs. The left lung contains two lobes compared to the three lobes of the right lung. The right lung is shorter than the left lung in the cranial caudal direction but wider in the lateral direction. Overall the total volume capacity of the right lung is typically greater than the capacity of the left lung. The Ansari-Bradley test was used to test the spread of the lung tissue elongation distribution compared to a lognormal distribution. The lung tissue elongation for the upper and lower lung was tested with a Kruskal-Wallis ANOVA test to determine if a significant difference existed between the right and left lung at the 95% confidence interval. The tissue elongations of the right and left lung, as well as the superior and inferior portions of the lungs, were independently analyzed to identify spatial hysteresis differences. Tissues with displacements of less than 5 mm were excluded from the analysis. To further characterize the tissue elongation, the 15\(^{th}\) and 85\(^{th}\) percentile values were reported to illustrate the small and large elongations, respectively.
Results

An Ansari-Bradley Test found the lung tissue elongation had a lognormal distribution ($p < 0.01$). The average elongation in the upper and lower halves of the left lung were $\zeta = 0.103 \pm 0.056$ and $\bar{\zeta} = 0.092 \pm 0.051$, respectively. The average elongation in the upper and lower halves of the left lung were $\zeta = 0.120 \pm 0.064$ and $\bar{\zeta} = 0.090 \pm 0.055$. The average elongation in the upper and lower halves of the right lung were $\zeta = 0.107 \pm 0.060$ and $\bar{\zeta} = 0.082 \pm 0.048$. In each lung and sub-region the elongation trend decreased for increasing tissue displacement. The 15th percentile elongations were 0.090±0.005 and 0.083±0.013 in the upper and lower left lung, respectively, and 0.092±0.006 and 0.085±0.013 in the upper and lower right lung, respectively, for motion magnitudes between displacements of 5 mm and 15 mm. The 85th percentile elongations were 0.187±0.037 and 0.203±0.053 in the upper and lower left lung, respectively, and 0.184±0.038 and 0.196±0.043 in the upper and lower right lung, respectively, for motion magnitudes between 5 mm and 15 mm. A summary of the elongation distribution at the 15th and 85th percentiles for tissue displacements up to 25 mm can be seen in Table 4.1. In each lung and sub-region, the elongation decreased with increasing tissue displacement. A Kruskal-Wallis ANOVA test found statistically significant differences between the lung tissue elongation in the upper and lower portions of the left lung ($p = 0.009$) for 85% of patients and the right lung ($p = 0.018$) in 83% of patients. The lung tissue elongation in both the upper and lower right and left lungs were found to be similar ($p = 0.355$) for the majority of the patients. Table 4.2 reports the percentage of patients displaying a statistically different comparison between the lung sub-regions. Figure 4.2 displays the distribution of maximum tissue displacement and the elongation distribution at increasing tissue motion intervals for all patients. The elongation
distribution for lung cancer and non-lung cancer patients is illustrated in Figure 4.3 for the right and left lungs.

Discussion

The characteristic breath method consistently produced a single breath that was highly representative of the breaths measured during the collection duration. An observable respiratory pattern was displayed in the characteristic breath. Figure 4.4 shows four examples of the characteristic breath for three lung cancer patients, one patient was imaged twice. The patient who was imaged twice (Figure 4.4a-b) had similar characteristic breaths in both sessions. The sessions occurred two weeks apart but the characteristic breaths had similar respiratory patterns. The characteristic breaths of this patient had a strikingly different pattern than the two other examples shown in Figure 4.4c-d. There was a unique characteristic breath for each patient.

The elongation distribution throughout the lung displayed characteristics that differed in the presence of lung cancer. Figure 4.5 displays two examples of lung cancer and two examples of non-lung cancer results that were typical of the observed results. The patient in Figure 4.5a had a stage 1A tumor in the left upper lung in the same location as the greater elongation values. The locally greater elongation values can be seen in Figure 4.5b where a stage 3A tumor was present in the right lower lung. The elongation distributions for the lung cancer patients in the local tumor region were different than for the non-lung cancer patients in similar locations. Figure 4.5c-d displays typical results for non-lung cancer patients. For these cases the elongation varied smoothly throughout the lung and did not exhibit large local variations. Despite an observable local difference, there was no statistically significant difference, at the 95% confidence interval, with respect to the average lung tissue elongation between lung cancer and
non-lung cancer patients (Kruskal-Wallis test) as shown in Figure 4.3. This suggests the lung compensated for the increased hysteresis of diseased tissue by reducing the hysteresis of healthy lung tissue.

The comparison between the upper right lung and upper left lung displayed statistically significant variation in 35% of patients. Only 22% of patients displayed a statistically significant difference between the lower right lung and lower left lung at the 95% confidence interval. This disparity between the upper and lower lung regions can be expected due to the relatively small motion magnitudes present in the upper lung compared to the lower lung. The motion variation was less for the lower right lung and lower left lung due to the increased motion magnitudes present there. As seen in Table 4.1, when the overall motion displacement increased, the average elongation was observed to decrease in magnitude. This inverse relationship shows the relative hysteresis component of lung tissue motion decreases as the motion displacement increases. When modeling lung tissue motion it would be possible to ignore hysteresis for sufficiently large displacements with only a marginal error in tissue motion characterization.

In 2008 a study by Boldea et al. reported hysteresis for five patients treated with external beam radiation for non-small cell lung cancer. They reported the hysteresis motion to be larger in the tumor volume than in healthy tissue which is in agreement with the results of this study. Furthermore the elongation was in agreement with the ratio of hysteresis magnitude to tissue trajectory length reported in previous studies.

**Conclusions**

The hysteresis behavior of breathing motion was analyzed using a motion model that describes breathing motion as a function of tidal volume and airflow. A characteristic breath was
defined to summarize individual patient’s breathing cycles in such a way that the breathing motion path could be defined without discontinuities. The elongation magnitude was relatively small, usually less than 25% of the tidal-volume generated tissue motion. Implications of these results are that in many cases, ignoring hysteresis would yield small errors in the tissue motion characterization. Therefore, when developing amplitude-based gating techniques, reviewing these data could be used to determine the consequences of ignoring hysteresis.
Figure 4.1: The tissue trajectory was calculated by the $\vec{a}$ and $\vec{b}$ vectors scaled by $v$ and $f$ respectively, which was calculated from the characteristic breath, and the angle between $\vec{a}$ and $\vec{b}$, $\theta$. 
Figure 4.2: Histograms displaying the distribution of the tissue displacement (a) and the distribution of the elongation at increasing tissue motion intervals (b).
Figure 4.3: Histograms summarizing the average distribution of the tissue elongation for the left and right lung across lung cancer, non-lung cancer, and combined patient data sets.
Figure 4.4: Airflow vs. tidal volume relationships for the entire breathing session (blue curves) and the unique characteristic breath (red curve) for one patient imaged in two separate sessions (a,b) and two additional patients (c,d).
Figure 4.5: Elongation maps of different patients with (a,b) and without (c,d) lung cancer. The elongation distribution varies smoothly in the non-lung cancer patients and displays regionally high elongation at the tumor sights in the lung cancer patients.
<table>
<thead>
<tr>
<th>Tissue Displacement</th>
<th>Left Upper Lung</th>
<th>Left Lower Lung</th>
<th>Right Upper Lung</th>
<th>Right Lower Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15&lt;sup&gt;th&lt;/sup&gt;</td>
<td>85&lt;sup&gt;th&lt;/sup&gt;</td>
<td>15&lt;sup&gt;th&lt;/sup&gt;</td>
<td>85&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>5 – 7.5 mm</td>
<td>0.097</td>
<td>0.238</td>
<td>0.099</td>
<td>0.271</td>
</tr>
<tr>
<td>7.5 – 10 mm</td>
<td>0.088</td>
<td>0.187</td>
<td>0.086</td>
<td>0.215</td>
</tr>
<tr>
<td>10 – 12.5 mm</td>
<td>0.091</td>
<td>0.172</td>
<td>0.079</td>
<td>0.178</td>
</tr>
<tr>
<td>12.5 – 15 mm</td>
<td>0.085</td>
<td>0.150</td>
<td>0.069</td>
<td>0.148</td>
</tr>
<tr>
<td>15 – 17.5 mm</td>
<td>0.094</td>
<td>0.156</td>
<td>0.070</td>
<td>0.138</td>
</tr>
<tr>
<td>17.5 – 20 mm</td>
<td>0.072</td>
<td>0.143</td>
<td>0.066</td>
<td>0.130</td>
</tr>
<tr>
<td>20 – 22.5 mm</td>
<td>0.081</td>
<td>0.121</td>
<td>0.063</td>
<td>0.117</td>
</tr>
<tr>
<td>22.5 – 25 mm</td>
<td>0.089</td>
<td>0.169</td>
<td>0.064</td>
<td>0.121</td>
</tr>
</tbody>
</table>

*Table 4.1:* Summary of the 15<sup>th</sup> and 85<sup>th</sup> percentile lung tissue elongation for increasing tissue displacement in each lung sub-region.
<table>
<thead>
<tr>
<th>Lung sub-region Comparison</th>
<th>Upper left vs. Lower left</th>
<th>Upper right vs. Lower right</th>
<th>Upper left vs. Upper right</th>
<th>Lower left vs. Lower right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistically different at 95%CI</td>
<td>85%</td>
<td>83%</td>
<td>35%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Table 4.2:* Percentage of cases showing significant difference between the respective comparisons.
Chapter 5: Investigation of a Breathing Surrogate Prediction Algorithm for Prospective Pulmonary Gating †

Abstract

Purpose: A major challenge of four dimensional computed tomography (4DCT) in treatment planning and delivery has been the lack of respiration amplitude and phase reproducibility during image acquisition. Implementation of a prospective gating algorithm would ensure that images would be acquired only during user-specified breathing phases. This study describes the development and testing of an autoregressive moving average (ARMA) model for human respiratory phase prediction under quiet respiration conditions.

Methods: A total of 47 4DCT patient datasets and synchronized respiration records were utilized in this study. Three datasets were used in model development and were removed from further evaluation of the ARMA model. The remaining 44 patient datasets were evaluated with the ARMA model for prediction time steps from 50 ms to 1000 ms in increments of 50 and 100 ms. Thirty five of these datasets were further used to provide a comparison between the proposed ARMA model and a commercial algorithm with a prediction time step of 240 ms.

Results: The optimal number of parameters for the ARMA model was based on three datasets reserved for model development. Prediction error was found to increase as the prediction time step increased. The minimum prediction time step required for prospective gating was selected to be half of the gantry rotation period. The maximum prediction time step with a conservative 95% confidence criterion was found to be 0.3 s. The ARMA model predicted peak inhalation and peak exhalation phases significantly better than the commercial algorithm. Furthermore, the commercial algorithm had numerous instances of missed breath cycles and falsely predicted breath cycles while the proposed model did not have these errors.
Conclusions: An ARMA model has been successfully applied to predict human respiratory phase occurrence. For a typical CT scanner gantry rotation period of 0.4 s (0.2 s prediction time step) the absolute error was relatively small, 0.06 ± 0.02 s at peak inhalation and 0.05 ± 0.04 s at peak exhalation. The application of the ARMA model for prospective pulmonary gating has been demonstrated.
Introduction

One of the principal applications of four dimensional computed tomography (4DCT) has been to provide breathing phase-gated image datasets for treatment planning. The images are typically acquired while the patient undergoes quiet or coached respiration. The image datasets are used to characterize the motion of the tumor and normal lung tissues due to breathing. A challenge in respiratory 4DCT is the lack of breathing amplitude and period reproducibility. This can lead to the acquisition of images that provide either redundant motion information or are acquired during an irregular breath and subsequently do not provide the data necessary for breathing motion characterization. The response in these cases is to repeat the scans, increasing the dose to the patient. A prospective gating algorithm that considered breathing cycle irregularities and acquired CT data only when the breathing cycle was in user-specified phases, including assessing whether the breath was representative of the patient’s normal breathing, would be more accurate and useful for 4DCT acquisition.

In 2005, Low et al. proposed a motion model that used tidal volume and airflow as surrogates for the breathing cycle. Their CT acquisition protocol used ciné mode CT, acquiring 25 CT scans over a 15 s period at each couch position using a reduced mAs to reduce the total CT dose. The relatively large number of scans was selected in order to assure that the patient breathed at least one representative breath during the scan acquisition. Because Low et al. were developing and evaluating a breathing motion model for quiet respiration, coaching was not used.

While the ciné protocol provided adequate image data for registration and subsequent motion modeling, there remained two issues that limited its utility. First, some scans were acquired during times when the breathing cycle was irregular. This yielded images that were not
useful but had still irradiated the subject. Secondly, the lack of synchronization between the breathing phase and scan acquisition meant that scans could not be acquired at specific phases such as peak inhalation and exhalation, when breathing motion artifacts were minimal. In principal, prospective pulmonary gating could be used to overcome both of these limitations.

Prospective pulmonary algorithms have been developed to support phase-based linear accelerator gating using different methods, including neural networks [146, 147], a sinusoidal model [148], local regression [122], root mean square of a periodic signal [149], mean positional tracking [150], elliptical shape tracking [151], and recently an interacting multiple model with a Kalman filtering [152]. Prediction errors have been the primary metrics used to evaluate prospective gating algorithms [153].

Neural network algorithms use multiple interconnected artificial nodes to model complex biological relationships. These algorithms are highly nonlinear and require a training period for the algorithm to learn which outputs are yielded from particular input combinations. The primary criticism of neural network algorithms is the extensive training period required to cover the typical range of outputs. Kakar et al [146] used a 5-layer neural network combined with fuzzy logic to develop a model that would associate breathing input at an earlier phase with a later phase. They tested the algorithm with 11 patients for coached and un-coached breathing with results showing greater root mean square error (RMSE) for the un-coached cases. In 2008 Murphy et al [147] investigated the need to apply a filter to the neural network. The study incorporated a least mean-squares (LMS) adjustment to the neural network input from training data to act as a fast back-propagation update (adaptive filtering). This allowed the layers (stages) of the network to be reduced to 2. The algorithm was tested on 30 patient datasets that used both free breathing and coaching. Results showed that without a prediction time-step the
algorithm was able to reconstruct the signal exactly, but had greatly increasing error for prediction times from 100 ms to 500 ms due to the lack of signal reproducibility.

The periodic nature of breathing has led some investigators to approximate the breathing cycle as a sinusoid. *Vedam et al.*[148] investigated fitting a sinusoidal curve to training data (sinusoidal model) and compared it to a least mean squares algorithm (adaptive filter model). Five patients were incorporated into the study and each participated in multiple studies so that over 60 sessions were collected with 30s duration for coached, un-coached, and visual feedback breathing. They concluded the adaptive filter model had smaller prediction errors than the sinusoidal model and coached breathing had smaller prediction errors than un-coached breathing.

*Ruan et al.*[122, 149-151] have conducted several studies for predicting respiratory motion. In 2007, twelve patients were evaluated for irregularities in breathing traces by comparing the RMSE with a modified cosine signal fit in a least-squares sense.[122] This method was able to reproduce the shape of the breathing trace but failed to account for breathing irregularities. The group next investigated a local regression method and compared it to a neural network with a Kalman filter.[149] They concluded that the local regression method had smaller prediction errors for long prediction time steps with low sampling rates. The mean position between the peak inhalation and peak exhalation phases was tracked in an attempt to define an average breathing amplitude.[150] In this study, the breathing amplitude was graphed against the amplitude at a later time corresponding to a delay proportional to the uniform sampling interval and the discrete time lag. The graph appeared as an ellipse when a sine wave was used to simulate the breathing cycle and had a similar elliptical shape for actual breathing cycles. The ellipse was then used to predict the breathing phase for one breath. The most recent work in this series conducted in 2009 expanded on the previous work to manage breathing irregularities.[151]
There were three stages in their process: real time phase estimation with ellipse tracking, pattern estimation, and filtering. The model was tested on simulated data and twelve patient datasets. While their results were good for the simulated data, patient data had phase prediction errors as large as 50% with significant errors in amplitude.

In 1963, Priban [154] showed that the variation between breath cycles was not entirely a random phenomenon. This work formed the basis for the development of a proper model to predict respiratory motion. For this model, the breathing cycle was a measurement of the tidal volume, allowing the signal to be considered a discrete or finite time signal. Respiration could be estimated using a linear function with respect to previous data samples within the signal.

The goal of the current study is to test an autoregressive moving average (ARMA) approach to predict the respiration amplitude and phase for a clinically relevant range of prediction steps. The algorithm was developed and tested using measured patient breathing cycles. The ARMA model is one of numerous linear forecasting models that was shown to operate successfully on a time series applications. [155]

While the ARMA model has not been previously applied to radiation oncology breathing predictions, it has been investigated in Magnetic Resonance Imaging (MRI) image reconstruction. [156] Time series prediction models such as the ARMA model should have as few parameters as possible to reduce sources of error. [155] However, the model should also have enough parameters to adequately describe the breathing signal. The main advantage of the ARMA model is in its use of relatively simple autoregressive (AR) and moving average (MA) terms to induce correlation between current and previous data while simultaneously incorporating weighted averages of the previous data. This model will likely perform better than
individually using AR and MA terms by utilizing fewer parameters to describe the signal while maintaining sufficient simplicity to avoid over-fitting.

Methods

This work was developed to support breathing motion modeling research that utilizes tidal volume as the breathing surrogate. The surrogate measures the breathing trace as a series of discrete volumetric measurements spaced 10 ms apart. A prediction model was developed to predict the surrogate measured signal amplitude and consequentially respiratory phase at an advanced time. To quantitatively access the success of the prediction model in accurately predicting respiratory phase a comparison was made between the predicted and observed phases.

Autoregressive Moving Average (ARMA)

The ARMA model is a combination of autoregressive and moving average terms. The autoregressive term represents a predicted signal amplitude $A$ at time $t + \Delta t$, $A_{t+\Delta t}^{ar}$, as an all pole (rational function with constant numerator) infinite impulse response (IIR) filter. \[155\]

$$A_{t+\Delta t}^{ar} = c + \varepsilon_{t+\Delta t} + \sum_{i=1}^{p} \phi_{i} A_{t-(i-1)\Delta t}$$

(5.1)

where $p$ is the AR model order, $\phi_{i}$ are the model parameters, $A_{t}$ is the current signal amplitude, $\varepsilon_{t+\Delta t}$ describes additive white Gaussian noise (AWGN) output error, and $c$ is a constant. This autoregressive function is responsible for the phase of the prediction signal amplitude at time $t + \Delta t$ with respect to the signal amplitude at time $t$. The moving average term represents the predicted signal amplitude, $A_{t+\Delta t}^{ma}$, as an all zero (non-rational function) finite impulse response filter (FIR). \[155\]

$$A_{t+\Delta t}^{ma} = \mu + \varepsilon_{t+\Delta t} + \sum_{i=1}^{q} \theta_{i} \varepsilon_{t-(i-1)\Delta t}$$

(5.2)
where \( q \) is the MA model order, \( \theta_i \) are the model parameters, \( \epsilon_{t+\Delta t} \) describes additive white Gaussian noise (AWGN) output error, \( \epsilon_{t-(i-1)\cdot\Delta t} \) corresponds to the input white noise errors, and \( \mu \) is an expectation value, which was set to 0 for this study. The moving average modeled the linear regression of the predicted and observed signal amplitude. Both of these terms are incorporated into the ARMA model as follows \[^{[155]}\]

\[
A_{t+\Delta t}^{arma} = c + \epsilon_{t+\Delta t} + \sum_{i=1}^{p} \varphi_i A_{t-(i-1)\cdot\Delta t} + \sum_{i=1}^{q} \theta_i \epsilon_{t-(i-1)\cdot\Delta t} \tag{5.3}
\]

The ARMA model in Equation 5.3 is characterized by the doublet \((p, q)\) where \( p \) is the order of the autoregressive term and \( q \) is the order of the moving average term.

**ARMA Parameters Optimization**

The Akaike Information Criterion (AIC) was used to determine the optimal combination of zeros and poles for the ARMA model acting on a breathing trace. \[^{[157]}\] The AIC is an analysis tool that measures how well a statistical model represents a physical system. The AIC tool consists of two terms; the number of parameters in the system \( k = (p+q+l) \) and the maximum likelihood \( L \) \[^{[157]}\]

\[
AIC = 2k - 2 \ln(L) \tag{5.4}
\]

The least-squares definition of maximum likelihood is described as \[^{[158]}\]

\[
L = \prod_{i=1}^{n} \left( \frac{1}{2\pi \sigma_i^2} \right)^{1/2} \exp \left( -\frac{1}{2} \frac{(A_{i}^{pred} - A_{i}^{obs})^2}{2\sigma_i^2} \right) \tag{5.5}
\]

where \( A_{i}^{pred} \) is the predicted \( i^{th} \) signal amplitude, \( A_{i}^{obs} \) is the observed \( i^{th} \) signal amplitude, and \( \sigma_i^2 \) is the variance at the \( i^{th} \) sample. Taking the natural log of Equation 5.5 yields \[^{[157]}\]

\[
\ln(L) = \ln \left( \prod_{i=1}^{n} \left( \frac{1}{2\pi \sigma_i^2} \right)^{1/2} \right) - \frac{1}{2} \sum_{i=1}^{n} \frac{(A_{i}^{pred} - A_{i}^{obs})^2}{2\sigma_i^2} = C - \frac{1}{2} \chi^2 \tag{5.6}
\]
where the first term can be called $C$, which is considered as a constant if and only if the observations in the dataset are consistent while the predictions vary (i.e. different model parameters), and $\chi^2$ is the commonly recognized chi-squared expression. As $C$ only varies with the observations it can be omitted as the intention of using the AIC was to investigate the optimal combination of $p$ and $q$. Substituting Equation 5.6 into Equation 5.4 yields a straightforward expression for the AIC in terms of the number of parameters in the system and chi squared. [157]

The final prediction error (FPE) was used as a second metric to identify if the model order was sufficient to describe the breathing signal. In this case, the FPE was incorporated in conjunction with the AIC to aid in the optimization of the number of ARMA parameters. For large sample sizes, the FPE is defined as

$$FPE = f \left(1 + \frac{2d}{m}\right)$$  \hspace{1cm} (5.7)

where $f$ was represented by a Euclidean Norm (loss function), $d$ is the number of model parameters ($p+q$), and $m$ is the number of samples in the data set which was on average over 45000 samples. Since $p$ and $q$ are independent variables in the ARMA model, the Euclidean Norm will have a Rayleigh distribution (chi distribution with 2 independent variables). This behavior will display an asymptote in the FPE in a similar fashion to the AIC. The optimal model order is the order that provides the FPE value closest to the asymptote.

**Hamming Window Filter**

Breathing cycles often drift slowly in time, causing difficulties for some predictive algorithms. The breathing trace was considered to have two components; a fast varying signal superimposed on a slowly varying signal (drift). The difference in frequency spectral characteristics of these components was used to design a real-time filter using a finite impulse response (FIR) design. In order to avoid the spectral leakage problem in the Fourier transform
when dealing with discrete signals and ringing effects due to sudden truncations, the signal was multiplied by a window function to modulate the signal by a single sinusoidal cycle to systematically taper the signal amplitude. This process significantly reduced spectral leakage and ringing effects. The filter selected here to remove slow drift was the Hamming Window Filter. The window output signal at sample $i$ was defined by

$$w(i) = 0.54 - 0.046 \cos \left( \frac{2\pi i}{N} \right), \quad 0 \leq i \leq N$$

(5.8)

where $N$ was the number of samples in the window length. The window length used in this study was 0.1 s or ten samples, selected after testing a range of window lengths on patient data.

**Signal Normalization and Gating**

The measured signals were proportional to the diaphragmatic expansion during respiration. The signal amplitude was normalized to the 85th percentile tidal volume of the training period to provide a better qualitative view of respiration amplitude and phase. To reduce small-scale undulations of the predicted breathing trace and consequently improve the accuracy of the predicted breathing phases, the ARMA prediction curve was smoothed using a 5th order polynomial applied over a 0.5 s sliding window centered on the point being smoothed. The location of peak inhalation was identified for each breath by finding where the slope of the curve changed sign. To avoid inadvertently identifying false peaks, a minimum amplitude difference from the previous peak exhalation was also used when identifying an inhalation peak. The threshold amplitude difference was selected as 30% of the normalized average signal amplitude. The method for identifying peak exhalation was identical to the method to identify inhalation. In order to compare results for different patients, each breathing cycle was evaluated using the signal amplitude percentiles. Normal signal amplitude, which correlates to quiet respiration, was
defined as the difference between the 85th and 5th tidal volume percentile. Maximum exhalation was defined at the 5th percentile.

While the ARMA model could be used to determine the peak time and signal amplitude, it was assumed that abnormal breathing peaks, defined either by amplitude or period, would be excluded when gating. A training period for the model was necessary to determine the percentiles used for signal amplitude normalization and subsequent gating of the remaining signal. Peaks with a magnitude and period in excess of 1.5 standard deviations of the mean magnitude and period defined in the training period, respectively, were designated as abnormal. The gating window was applied to the filtered breathing trace.

Data Collection and Phantom Study

The breathing cycle data were acquired using a cylindrical bellows-shaped tube (Lafayette Instrument Co., model 76513NM10) wrapped around the patient’s abdomen. The belt was sealed so the air pressure decreased and increased during inhalation and exhalation, respectively. The air pressure was measured by a pressure transducer that provided a voltage signal proportional to the internal air pressure and the voltage signal was monitored using an analog-to-digital converter that was sampled every 10 ms. The voltage signal from this apparatus has been previously shown to be proportional to tidal volume. The bellows system was used to acquire breathing cycle data from 47 patients while they underwent research 4DCT procedures. Each patient was requested to breathe normally and quietly.

The ARMA algorithm was compared against a commercial prospective breathing algorithm that is used to identify breathing peaks in real time and is installed in a commercial Philips Brilliance 64 Slice CT simulator. Because the prospective gating algorithm was being tested and not image acquisition, the images were not analyzed. The scanner required a real-time
breathing signal for analysis. To provide these data, the bellows system was attached to a 
dynamic phantom system developed in our department. The phantom was moved by a 
distance proportional to the breathing tidal volume. The phantom had sub-millimeter dynamic 
positioning accuracy, corresponding to a breathing cycle simulation accuracy of less than a few 
percent. The CT scanner was operated using the prospective pulmonary axial protocol. The 
bellows was exercised by the stage during CT acquisition to provide the real-time patient 
breathing signals. The recorded breathing signal and the tags associated with peak inhalation 
and peak exhalation phases were exported from the CT scanner at the conclusion of the session. 
The prediction time step of the commercial algorithm was a fixed 240 ms.

**Patient Data**

Three of the 47 patient datasets were reserved to determine the order of the autoregressive 
term ($p$) and the order of the moving average term ($q$). Each was selected because it represented 
the range of breathing frequencies and amplitudes. One dataset had both an amplitude and 
frequency near the average of the 47 datasets, one had a relatively high frequency and small 
amplitude, and one had a relatively low frequency and large amplitude. After determination of 
the ARMA model parameters, these patient breathing datasets were no longer used in the study. 
The remaining 44 patients were used to test the model. To compare the model with the 
commercial peak detection prediction, 35 of these patients were selected for use with the CT 
scanner. The sampling frequency for the ARMA patient datasets was set at 100 Hz. The 
sampling frequency for the commercial algorithm comparison patient datasets was set at 500 Hz.

**Prediction Process**

The patient breathing dataset was first filtered with a Hamming window filter and the 
first thirty seconds of the signal were used to train the ARMA algorithm. The training period
length was determined by increasing the period from 10 s to 120 s in 10 s increments. The coefficients of the ARMA polynomials, the volume percentiles, and the phase statistics were determined within the training period. The ARMA signal was calculated using the model coefficients and a selected prediction time step while the filtered signal moved in time. When peaks were detected, they were included if they matched a pre-defined gating window criterion of 1.5 standard deviations from the means of both the period and amplitude. The prediction error was evaluated for prediction time steps from 0.05 s to 1.0 s. The overall workflow of the prediction model development is shown in Figure 5.1.

The commercial algorithm was proprietary so the prediction method for this model was not known. When the ARMA model prediction was compared against the commercial prediction algorithm, a prediction time step of 240 ms was used to coincide with the commercial prediction time step.

**Quantifying Prediction Error**

To aid in interpreting the results, one breath cycle from patient #6 is shown in Figure 5.2 where peak inhalation occurs near 0.9 s and the nomenclature used in this work is shown. The sample at \( t_i \) is the current time and \( \Delta t \) is the prediction time step, which is the amount of time ahead for which the prediction is made. The algorithm is designed to be used to predict the time at which the patient would be at a specific breathing phase. An example of peak inhalation is selected to evaluate the algorithm performance. If the algorithm was used to acquire a CT scan at peak inhalation, the prediction time step would be set to half the CT rotation time plus the system latency and time to account for model errors. Once peak inhalation had been predicted by the ARMA model, the scanner would be instructed to acquire images at half of a full gantry rotational period \((0.5*\pi_{360})\) before the predicted peak. The start and stop time are labeled in
Figure 5.2 as \( t_{on} \) and at \( t_{off} \), respectively. The minimum duration of the scan is equal to \( t_{off} - t_{on} \) which is the time it takes the scanner to perform a full 360\(^\circ\) rotation (\( t_{360^\circ} \)). The difference between the predicted and actual peaks is termed \( e_t \). Positive and negative errors correspond to predicted peaks occurring after and before the actual peak, respectively. If \( e_t > 0 \), the system would begin scanning but would not have acquired 180\(^\circ\) prior to peak inhalation. The acquired image would be suboptimal and the image acquisition might need to be repeated, leading to excess delivered dose. If \( e_t < 0 \), the scanner might be left on until the patient passed peak inhalation and \( t_{360^\circ}/2 \) further. Therefore, the error in peak position needed to be as small as possible.

Model performance was evaluated to determine how often the predicted peak was within half the scanner rotational period from the measured peak. In other words how often would the observed peak occur between \( t_{on} \) and \( t_{off} \), when the interval \( t_{off} - t_{on} \) was centered about the predicted peak. The prediction error relative to the scanner rotational period was represented by \( \eta \) and characterized by

\[
\eta = \frac{\Delta t - e_t}{t_{360^\circ}} \tag{5.9}
\]

There are three values of \( \eta \) that are of particular interest: \( \eta = 0, \frac{1}{2}, 1 \). In the absence of prediction error (\( e_t = 0 \), i.e. the prediction peak was in the exact location as the observed peak, the value of \( \eta \) will be \( \frac{1}{2} \). If the prediction was too early such that the prediction time error is equal in magnitude to the prediction time step (\( e_t = \Delta t \), so \( \eta = 0 \)) the scanner will not capture the desired peak in a single rotation and will need additional rotations to capture the peak. Conversely the other extreme has the prediction time error in the opposite direction (\( e_t = -\Delta t \)). In this case \( \eta = 1 \) so it would not be possible to capture the measured peak as it occurred much earlier than the predicted peak. The ARMA model was evaluated at increasing prediction time
steps and as long as 95% of the predictions had an interval of $0 < \eta < 1$, the prediction would be more than adequate for image acquisition of the desired respiratory phase.

**Results**

Figure 5.3 shows an example of an AIC curve for the normal breathing frequency model development patient. The other two patients used for the model development displayed similar trends. The results from the AIC test exhibit an asymptote at -16 with the closest value to the asymptote occurring at high model order combinations of $p$ and $q$. Selection of the order combination was done by evaluating the AIC, FPE, and the percent fit (less than 5% variation from the original data set) for a small prediction step of 0.01 s (one sample). Table 5.1 summarizes the results of the AIC, FPE, and percent fit for 3 combinations of the model order for the patient shown in Figure 5.3. The selected ARMA parameters of $p=2$ and $q=5$ provided the smallest number of model parameters at the smallest AIC and FPE values which made them the optimal selections.

Using an ARMA ($p=2, q=5$) model, the remaining 44 patient data sets were analyzed as functions of prediction time steps in order to find how long in time the algorithm was able to accuracy predict specific breathing phases. Figure 5.4 shows the prediction time error for predicting peak inhalation (a) and exhalation (b) as a function of prediction time step for each patient.

The magnitude of the time error typically increased as a function of prediction time step. While the magnitude of the prediction time error increased with increasing prediction time step, the same relationship could not be seen for the direction of the prediction time error. Furthermore Figure 5.4 shows the greater variability of the prediction time error for maximum exhalation.
Patients typically spend more time at exhalation, so the exhalation peak is less well defined than the inhalation peak. For most patients, a prediction time step of 0.4s resulted in prediction time errors of greater than 0.4s, implying that, if the scanner was going to be triggered such that the mid-scan time was at peak inhalation, the 0.4s prediction time did not provide sufficient latitude to ensure that the scanner would image peak inhalation. Figure 5.5 shows the mean and standard deviation of η as a function of prediction time step. Peak inhalation has smaller η values than the peak exhalation with considerably less variability for prediction time steps greater than 0.3 s. Figure 5.6 compares the prediction error for the commercial prediction algorithm and the ARMA algorithm (240 ms prediction time step) at peak inhalation and exhalation for the 35 patient datasets.

In addition to evaluating peak prediction errors, there were two cases that were examined; a false breath and a missed breath. A false breath was defined as a predicted maximum inhalation and corresponding maximum exhalation tag occurring within a measured respiratory cycle. A missed breath was defined as a lack of prediction tags for a measured breath. One of the differences between the ARMA model and commercial model evaluations was the inability of the commercial model to detect small breathing amplitudes in 9 patients. In addition, the commercial model inaccurately identified breaths. The commercial algorithm missed four valid breathing cycles and falsely recorded thirteen cycles with four patients having more than one false peak. One patient dataset had both missed and falsely identified peaks. The ARMA (2,5) algorithm did not falsely identify or miss a peak. Figure 5.7 compares the results of the commercial algorithm and ARMA model predictions. For Figure 5.7a, breath cycle were missed by the commercial algorithm at 37.8 s and 40.4 s. Figure 5.7b shows an example of a false breath that was recognized starting at 38.8 s and ending at 39.3 s. A summary of the number of
false breaths and missed breaths for the commercial algorithm and the ARMA algorithm is reported in Table 5.2.

**Discussion**

For a prediction time step equal to half of the time required to perform a full 0.4 s CT gantry rotation (equivalent to 0 s latency and no time to limit the probability that \( e_t > 0 \)), the CT scanner would have sufficient time to have rotated 180° at the time of peak inhalation. The approximation of 0 s latency was close to the quoted system latency time of 15 ms quoted by a commercial vendor. With current CT scanners capable of completing a full gantry rotation in 0.4 s or less, the minimum prediction time step needed to allow gating would be 0.2 s. Reducing the gantry rotation period will reduce the prediction time step required to predict the respiratory phase then trigger the scanner to capture the desired respiratory phase. The ARMA (2,5) model performed better for small prediction time steps compared to larger prediction time steps. Using Figure 5.4 as a reference, when the prediction step was 0.2 s, the ARMA (2,5) showed an error of 0.06 ± 0.02 s for the 44 tested patients. At peak exhalation, the error was 0.05 ± 0.04 s. The sign of the error was important because if \( e_t > 0 \), the predicted peak time occurred later than the actual time so images would not correspond to the selected phase. Both of these error results are reduced for smaller prediction time steps (faster gantry rotation periods). If \( e_t << 0 \), the beam on time would be significantly greater to acquire the images. By keeping 95% of the errors less than 0.2 s for a 0.4 s gantry rotation period, the desired peak will most likely be captured in the scanning window and extra beam on time will be reduced in the process. The maximum prediction time step that would have a 95% probability of capturing the peak was 0.3 s with a 95% confidence criterion for both maximum inhalation and maximum exhalation. The value of
η had greater variability for maximum exhalation than inhalation because exhalation exhibited a shallower peak. These results were specifically for a 0.4 s gantry rotation period.

In the algorithm comparison the ARMA (2,5) outperformed the commercial algorithm in every case. Furthermore, the ARMA (2,5) model did not miss or falsely record a breath cycle while the commercial algorithm had numerous instances of both. For peak inhalation the error in the peak inhalation was 0.03 ± 0.5 s for the commercial algorithm and 0.001 ± 0.01 s for ARMA (2,5). For peak exhalation, the errors were 0.36 ± 1.21 s and 0.003 ± 0.01 s for the commercial algorithm and the ARMA (2,5) respectively. The prediction time step for these patients was 0.24 s. Because the commercial algorithm had error significantly greater than the prediction time, it was shown to be inappropriate for prospective gating.

Conclusions

An ARMA model, in conjunction with Hamming filtering, has been optimized to predict human respiratory phase and tested at peak inhalation and exhalation phases. The validity and maximum prediction time step of the model were investigated with 44 patient breathing traces measured using a cylindrical bellows-shaped tube. For a gantry rotation period of 0.4 s, the minimum required prediction time step would be 0.2 s. At this prediction time step, the model had relatively small errors. This demonstrates that the model can be used with modern fast CT scanners. The small errors will allow additional time to account for system latency greater than the latency of the CT scanner used in this study. For comparison with a commercial algorithm, the Washington University 4D Phantom was used to provide real-time breathing signals to a Philips Brilliance 64 Slice scanner. Tags representing the peak inhalation and peak exhalation were exported from the operator consol and were compared with the results of ARMA (2,5) for
the same breathing trace. The ARMA (2,5) was found to be significantly better than that commercial algorithm. Based on these results, prospective pulmonary gating has been shown to be possible for modern 4D CT simulation.
Figure 5.1: Workflow of the prediction process.
Figure 5.2: Illustration of the nomenclature used in this work. This is the peak of a single inhalation. The solid and dotted curves indicate the measured and predicted breathing signals respectively.
Figure 5.3: Results of an AIC test for a model development patient.
Figure 5.4: Average prediction time error $e_t$ in seconds for peak inhalation (a) and peak exhalation (b) of the ARMA (2,5) prediction as a function of prediction step. Data are shown for the 44 evaluated patients.
Figure 5.5: Average $\eta$ with the 95% confidence window for 44 patients at increasing prediction time steps. The solid line curve represents maximum inhalation while the dashed line curve represents maximum exhalation.
Figure 5.6: Histograms of the 240 ms prediction error for peak inhalation and exhalation for the ARMA model and commercial algorithm for 35 patients. (a) Peak inhalation for the commercial algorithm. (b) Peak exhalation for the commercial algorithm. (c) Peak inhalation for the ARMA algorithm. (d) Peak exhalation for the ARMA algorithm.
Figure 5.7: An example of a patient data set showing the comparison of the commercial algorithm and the ARMA model predictions.
<table>
<thead>
<tr>
<th>(p,q)</th>
<th>AIC</th>
<th>FPE</th>
<th>Percent Fit (&lt;5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1,0)</td>
<td>-10.768</td>
<td>1.472 x 10^{-5}</td>
<td>68.2%</td>
</tr>
<tr>
<td>(1,1)</td>
<td>-11.975</td>
<td>4.575 x 10^{-6}</td>
<td>68.76%</td>
</tr>
<tr>
<td>(2,5)</td>
<td>-15.654</td>
<td>1.521 x 10^{-7}</td>
<td>84.51%</td>
</tr>
</tbody>
</table>

*Table 5.1*: AIC, FPE, and percent fit results for three particular ARMA parameter combinations for the process outlined in Figure 5.1 and Equation 5.3.
<table>
<thead>
<tr>
<th>Prediction Model</th>
<th>Missed Breath</th>
<th>False Breath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Algorithm</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>ARMA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5.2: Number of patients with missed or falsely tagged breath cycles for both prediction models.
Chapter 6: Modeling and Incorporating Cardiac-induced Lung Tissue Motion in a Breathing Motion Model‡

Abstract

Purpose: The purpose of this work is to incorporate cardiac-induced lung motion into an existing breathing motion model.

Methods: Our proposed cardiac-induced lung motion model represents the lung tissue’s specific response to the subject’s cardiac cycle. The model is mathematically defined as a product of a converging 9th order polynomial function \( h \) of the cardiac phase \( (c) \) and the maximum displacement \( \gamma(\vec{X}_0) \) of each voxel \( (\vec{X}_0) \) among all the cardiac phases. The function \( h(c) \) was estimated from cardiac-gated MR imaging of 10 healthy volunteers using an Akaike Information Criteria (AIC) optimization algorithm. For each volunteer, a total of 24 short-axis and 18 radial planar views were acquired on a 1.5 T MR scanner during a series of 12 – 15 second breath-hold maneuvers. Each view contained 30 temporal frames of equal time-duration beginning with the end-diastolic cardiac phase. The frames in each of the planar views were re-sampled to create a set of 3D anatomical volumes representing thoracic anatomy at different cardiac phases. A 3D multi-resolution optical flow deformable image registration algorithm was used to quantify the difference in tissue position between the end-diastolic cardiac phase and the remaining cardiac phases. To account for image noise, voxel displacements whose maximum values were less than 0.3 mm, were excluded. In addition, the blood vessels were segmented and excluded in order to eliminate MRI artifacts caused by blood-flow.

Results: The proposed model reduced the cardiac-induced lung tissue motion for each of the volunteers. The average cardiac-induced lung motion for tissue displacements greater than 0.3
mm was found to be $0.87 \pm 0.76$ mm and $1.09 \pm 1.19$ mm in the left and right lungs, respectively. The average model residual error for the ten healthy volunteers was found to be $0.31 \pm 0.09$ mm in the left lung and $0.44 \pm 0.19$ mm in the right lung for tissue displacements greater than 0.3 mm. The relative error decreased with increasing cardiac-induced lung tissue motion. While the relative error was $> 60\%$ for sub-millimeter cardiac-induced lung tissue motion, the relative error decreased to $< 5\%$ for cardiac-induced lung tissue motion that exceeded 10 mm in displacement.

**Conclusions:** Our studies showed that modeling and including cardiac-induced lung motion improved breathing motion model accuracy.
Introduction

Breathing motion significantly impacts the radiation therapy treatment planning and delivery process.\textsuperscript{[160]} It can arise from voluntary, involuntary, and semi-voluntary physiological factors. One solution to account for the breathing-induced lung tissue motion has been to employ lung motion models for planning and treatment\textsuperscript{[64-66, 73, 132, 133, 138, 148, 153, 161-163]}. Lung and lung tumor motion models have been developed based on lung tissue elasticity\textsuperscript{[132, 133, 138, 161, 163]}, respiratory phase\textsuperscript{[64, 65, 148, 153, 162]}, and biomechanical tissue properties.\textsuperscript{[66, 73]} These models, however, did not address the lung motion induced by the heart’s pulsatile motion. There have been studies that evaluated breathing induced cardiac motion\textsuperscript{[45, 164-166]}, but no specific modeling efforts has been developed to quantify and report cardiac-induced lung motion.

Cardiac motion is uncorrelated to the breathing cycle, so cardiac motion may appear as noise in breathing motion measurements that consist of repeated CT scans, such as those used by Low et al.\textsuperscript{[167]} Subsequently, breathing motion model accuracy will be degraded by this apparently random motion component. Cardiac-induced lung tissue motion has been measured using 4D fluoroscopy and observed to be oriented in the lateral direction with a magnitude in the range of 1 – 4 mm.\textsuperscript{[65]}

The motion of the heart during the different cardiac phases consists of radial, longitudinal, and circumferential displacements.\textsuperscript{[168-171]} The base of the heart contracts, ejecting blood from the ventricles. This contraction changes the shape and volume of the heart, causing the lung to expand and slide against the heart. The apex of the heart contracts less than the base but includes a circumferential torsion.\textsuperscript{[172]} The maximum myocardium displacement of the heart during the different phases of a cardiac cycle was reported to be approximately 30 mm, greater
than the 1 – 4 mm of lung-induced cardiac motion. Such large displacements may also lead to substantial cardiac-induced lung motion. Modeling the cardiac-induced lung motion and incorporating the cardiac-induced lung motion into a breathing lung motion model forms the focus of this paper.

Methods

In this section, we describe the mathematical formulation to model cardiac-induced lung tissue motion. The formulation, when incorporated into the 5D breathing motion model accounts for cardiac-induced lung motion and presumably will improve the breathing motion model. To characterize the morphological changes in lung anatomy during the cardiac cycle, we employed a cardiac-gated MRI protocol. A 3D optical flow image registration algorithm was used to find the deformation vectors of the lung tissue in Cartesian space. The temporal dependence of the deformation vectors on the cardiac cycle was estimated with a converging polynomial whose order was optimized with an Akaike Information Criteria (AIC) method. The model was designed as a linear relation between the maximum tissue displacement of each voxel and the cardiac phase. The model performance was assessed by comparing the model residual error against the uncompensated cardiac-induced lung tissue motion.

5D Breathing Motion Model

The breathing motion model that we were modifying was previously developed by Low et al. The model utilized airflow $f$ and tidal volume $v$ as time-dependent surrogates and the internal lung tissue position ($\vec{X}$) was determined by the expression:
\( \tilde{X}(v, f; \tilde{X}_0) = \tilde{X}_0 + \tilde{\alpha}(\tilde{X}_0)v + \tilde{\beta}(\tilde{X}_0)f \)  

(6.1)

where \( \tilde{X}_0 \) was the position of the tissue at zero tidal volume and airflow. \( v \) and \( f \) scaled the tissue specific vectors \( \tilde{\alpha} \) and \( \tilde{\beta} \) which determined the motion direction and magnitude for the volume filling and hysteresis components, respectively.

The accuracy of determining \( \tilde{\alpha} \) and \( \tilde{\beta} \) in the 5D breathing motion model was previously demonstrated in a cohort of 50 subjects. \(^{[67]}\) Model and measured tissue position differences were used by Zhao et al \(^{[68]}\) to evaluate the 5D model precision. They showed that the absolute discrepancy of the 5D breathing motion model was less than 2.1 mm for 90\% of the voxels in the subject cohort, \(^{[68]}\) but their measurements may not have been of sufficient resolution to detect increased modeling errors near the heart. More recently, Low et al \(^{[167]}\) improved the breathing motion model measurement technique and saw increased motion model error near the heart that might be decreased if a cardiac motion model term was incorporated into the breathing motion model.

**Cardiac-Induced Lung Motion Model**

To model the effect of the cardiac motion on lung tissue, we introduced a new term to Equation 6.1. For clarity, all of the variables and terms used in this section are defined in Table 6.1. We modeled the motion as follows:

\[ \tilde{C} = \tilde{\gamma}(\tilde{X}_0)h(c), \]  

(6.2)

where \( \tilde{C} \) represented the cardiac-induced lung motion at any cardiac phase, and \( \tilde{X}_0 \) was the position of the tissue at \( v = f = 0 \) and at the beginning of the cardiac cycle \( (c = 0) \). \( h(c) \) described
the temporal motion envelope of all of the cardiac-induced motion and \( \vec{y}(\vec{X}_0) \) described the local motion magnitude and direction. \( h(c) \) was defined such that \( h(0)=0 \) and the maximum value for \( h \) was 1.

From a biomechanical perspective, the term \( \vec{y} \) represented the tissue specific response to the cardiac pulsation. The term was assumed to be independent of breathing-induced motion and so the term was added to the 5D model shown in Equation 6.1. In Cartesian coordinates, \( \vec{y} \) was written as

\[
\vec{y} = ||\vec{y}|| (\cos \theta_x \hat{i} + \cos \theta_y \hat{j} + \cos \theta_z \hat{k}),
\]

where \( ||\vec{y}|| \) was the maximum displacement of the lung tissue during the cardiac cycle and was formulated as follows:

\[
||\vec{y}|| = \max \left\{ ||\vec{u}_p \hat{i} + \vec{v}_p \hat{j} + \vec{w}_p \hat{k}|| \right\}_{c=1}^T,
\]

where the term \((\vec{u}, \vec{v}, \vec{w})\) indicated the deformation vectors for each voxel across the cardiac frames in the Cartesian coordinate system \((\hat{i}, \hat{j}, \hat{k})\). The superscript \( T \) denotes the total number of cardiac frames \((c)\) in a single cardiac cycle. The values of \((\theta_x, \theta_y, \theta_z)\) were determined from:

\[
\theta_x = \cos^{-1} \left( \frac{||\vec{u}_p||_{\text{max}}}{||\vec{y}||} \right), \quad \theta_y = \cos^{-1} \left( \frac{||\vec{v}_p||_{\text{max}}}{||\vec{y}||} \right), \quad \theta_z = \cos^{-1} \left( \frac{||\vec{w}_p||_{\text{max}}}{||\vec{y}||} \right).
\]

Figure 6.1 illustrates the coordinate system of the cardiac-induced lung motion model.

The temporal term \( h(c) \) was represented in the form of a converging polynomial that fitted the deformation vector magnitudes normalized to the maximum tissue displacement. The polynomial order was chosen as the lowest order polynomial function capable of describing the
normalized deformation vector magnitudes while satisfying the AIC \cite{157} For this study, the AIC was expressed in terms of the number of parameters ($k$) in the polynomial fit of $h$ and the maximum likelihood ($L$). The expression for the AIC and the maximum likelihood are shown in Equation 6.6 and 6.7 respectively. \cite{157}

$$AIC = 2k - 2 \ln(L),$$ \hspace{1cm} (6.6)

$$L = \prod_{c=1}^{T} \left( \frac{1}{2\pi\sigma_c^2} \right)^{1/2} \exp \left( -\frac{1}{2} \sum_{c=1}^{T} \frac{(h_c^{\text{fit}} - h_c^{\text{m}})^2}{2\sigma_c^2} \right).$$ \hspace{1cm} (6.7)

In Equation 6.7, $\sigma_c^2$ is the variance at a given cardiac frame, $h_c^{\text{fit}}$ is the $h$ value from the polynomial fit at a given cardiac frame, and $h_c^{\text{m}}$ is the measured $h$ value at a given cardiac frame. An expression for the AIC in terms of chi-squared ($\chi^2$) was derived by taking the natural log of the maximum likelihood expressed in Equation 6.7. \cite{157}

$$\ln(L) = \ln \left[ \prod_{c=1}^{T} \left( \frac{1}{2\pi\sigma_c^2} \right)^{1/2} \right] - \frac{1}{2} \sum_{c=1}^{T} \frac{(h_c^{\text{fit}} - h_c^{\text{m}})^2}{2\sigma_c^2} = A - \frac{1}{2} \chi^2,$$ \hspace{1cm} (6.8)

Where the first term in Equation 6.8, $A$, is a constant under the condition of consistent measurement data, (i.e., the number of model parameter varies but the measured data stays the same) and the second term is the chi-squared expression. The AIC was used to find the fewest number of parameters needed to describe the behavior of $h$ over the cardiac cycle, since $A$ was independent of the fit it was omitted from the AIC expression. This allowed the AIC to be a straightforward function of the number of parameters in the polynomial fit of $h$ and the chi-squared expression. \cite{50}
A polynomial function was chosen to maintain a strictly temporal relationship between cardiac frame and lung tissue motion. The deformation vectors of each voxel were normalized to the maximum displacement of that voxel over the cardiac cycle. The first cardiac frame of $h$ was constrained to be 0 since this cardiac frame was taken as the reference image in the deformable image registration algorithm. The value of $h$ was made to vary between 0, corresponding to the reference cardiac phase (end-diastolic), and 1 which corresponded to the cardiac frame with greatest tissue motion. The volunteer specific ($s$) polynomial behavior of $h$ for each voxel ($n$) followed the form:

$$h_s^s(c) = \sum_{j=0}^{k} m_j c^j$$  \hspace{1cm} (6.9)$$

A mean of the polynomial coefficients for each voxel was calculated to produce a single new polynomial for all of the voxels within the lung.

$$h_s(c) = \frac{1}{n} \sum_{j=1}^{n} h_k^s(c)$$  \hspace{1cm} (6.10)$$

This procedure to determine $h$ was individually done for the right and left lungs. The limit of $\mathbf{C}$ provided in this section was mathematically undefined in the event that a given voxel didn’t move, $\|\mathbf{C}\| = 0$. If a voxel did not experience cardiac-induced lung motion, $\|\mathbf{\tilde{y}}\|$ and $h$ would be equal to 0 and the angular components of $\mathbf{\tilde{y}}$, $(\theta_x, \theta_y, \theta_z)$ would be undefined. Incorporating the cardiac-induced lung motion term ($\mathbf{\tilde{C}}$) from Equation 6.2 into Equation 6.1 provided:

$$\mathbf{X}(v, f, h; \mathbf{\tilde{X}}_0) = \begin{cases} \mathbf{\tilde{X}}_0 + \tilde{a}(\mathbf{\tilde{X}}_0) v + \tilde{\beta}(\mathbf{\tilde{X}}_0) f \quad & \exists \mathbf{\tilde{C}} \mid \|\mathbf{\tilde{y}}\| = 0 \\ \mathbf{\tilde{X}}_0 + \tilde{a}(\mathbf{\tilde{X}}_0) v + \tilde{\beta}(\mathbf{\tilde{X}}_0) f + \tilde{\mathbf{\tilde{C}}} \quad & \exists \mathbf{\tilde{C}} \mid \|\mathbf{\tilde{y}}\| > 0 \end{cases}$$  \hspace{1cm} (6.11)$$

**Data collection**
To quantify cardiac-induced lung motion, we used an MRI protocol to measure lung tissue motion during the cardiac cycle. Ten healthy volunteers were imaged with an Avanto 1.5 T Siemens MRI scanner (Siemens Healthcare, Erlangen, Germany). The imaging protocol closely followed a previously established sequence by Ennis et al. [174]. The protocol was a balanced steady-state free precession sequence with an echo time of 1.6 ms and a repetition time of 3.2 ms. The field of view was 360 mm. The volunteers were instructed to perform a series of 12 - 15 second breath holds at mid-exhalation for each view. The views were acquired with electrocardiogram (ECG) gating to monitor the cardiac phase. For each view, ~14 cardiac cycles of data were acquired with each breath hold and were retrospectively binned using the ECG tags to provide 30 equal time duration cardiac frames to represent a single cardiac cycle. The first cardiac frame represented the thoracic anatomy at the end diastolic cardiac phase and was timed to coincide with the closure of the mitral valve. A total of 24 planar views in the short axis orientation were taken with 3.5 - 4 mm slice thickness from the mitral valve plane at the base of the heart to the ventricular apex plane at the apex of the heart. The slice thickness was directly related to the short axis length of the volunteer’s heart. The short axis views were supplemented by 18 radial views at 20° increments centered about the plane intersecting the mitral valve and the ventricular apex. The short axis images and the radial images were re-sampled to form a 3D volume representing the thorax anatomy at each cardiac frame and provided the input for a 3D deformable image registration algorithm. The right and left lung volumes were masked with a region growing algorithm to only consider lung tissue in the analysis. Large blood vessels and rigid bronchial structures were also removed to account for MRI perfusion artifacts.

Image Registration
We employed a Graphics Processing Unit (GPU) based multi-resolution 3D optical flow algorithm.\cite{175,176} Mathematically, the optical flow image registration method was based on the Taylor Series approximation and has been well defined in literature.\cite{175,176} Solving for this Taylor series approximation, we employed a Jacobian iterative solver\cite{175,176} that was computationally accelerated to determine the 3D volumetric displacement.

The registration steps were: For each subject, the 3D anatomy at the end-diastole cardiac phase was taken as a reference and the deformation vectors were determined from the reference 3D anatomy to the 3D anatomies at different cardiac phases. A set of 3D anatomies at multiple lower resolutions were generated for both the reference and the target 3D anatomy. The registration was performed for the reference and the target 3D anatomy at the lowest 3D resolution level. The result of this registration was up-scaled and provided as initial input for registering the reference and the target 3D anatomy at the next 3D resolution level. The process continued until the reference and the target 3D anatomy were registered at the original 3D resolution level.

Model generation

The results of the multi-resolution 3D optical flow registration provided the deformation vectors for each voxel in the lung. The segmented lung volumes without internal blood vessels provided the regions of interest in the thoracic anatomy. The maximum displacement over the cardiac cycle relative to the first frame for each voxel was identified. This was used to normalize the response of the voxel to the cardiac cycle over the 30 cardiac phases. A converging polynomial was fit to the normalized response for each voxel from the reference phase ($h=0$) to the maximum displacement phase ($h=1$). The polynomial coefficients of each voxel were
averaged over all voxels in the lung to express a single polynomial for the lung. This was used to scale the maximum displacement along the direction of the maximum displacement of each voxel over the cardiac cycle to create the cardiac-induced lung motion model.

**Statistical Distribution**

The displacement magnitude and direction for each lung voxel were analyzed to check the data distribution and assess statistical significance. An Ansari-Bradley test was selected as a statistical metric with which to assess the distribution of $\|\vec{g}\|$ and the model residual error. The Ansari-Bradley test is a nonparametric hypothesis test of equal variances. The distribution of $\|\vec{g}\|$ was checked at the 95% confidence level.

**Results**

The accuracy of the deformable image registration algorithm was checked by using the calculated deformation vectors to warp each cardiac frame back to its respective reference. The discrepancy between the reference cardiac frame and subsequent cardiac frames with this method was observed to be negligible. Figure 6.2 shows the overlay of the reference and one of the cardiac frame images for both warped and un-warped cases. The deformable image registration algorithm was shown to be qualitatively accurate. A quantitative analysis for the accuracy of the deformable image registration algorithm has been described in detail in Santhanam et al [177].

The average cardiac-induced lung motion for tissue displacements greater than 0.3 mm was $0.87 \pm 0.76$ mm and $1.09 \pm 1.19$ mm in the left and right lungs, respectively. The average model residual error for the ten healthy volunteers was found to be $0.31 \pm 0.09$ mm in the left
lung and 0.44 ± 0.19 mm in the right lung for tissue displacements greater than 0.3 mm. Figure 6.3 shows the reduction in cardiac-induced lung motion achieved with the model for a short axis view of the right and left lung. Figures 6.3a and 6.3b illustrate the distribution of the cardiac-induced lung tissue motion in the right and left lungs, respectively, showing that the cardiac-induced motion was sub-millimeter for most of the lung tissue. Figures 6.3c and 6.3d show the corresponding distribution of the model residual error, defined as the difference between the registration-measured motion and the motion described by \( \hat{C} \), for the views in Figure 6.3a and 6.3b, respectively. Every voxel had less model residual error compared with the magnitude of cardiac-induced lung tissue motion. This is illustrated in Figure 6.4 by comparing the distribution of the cardiac-induced lung motion and the model residual error. Figure 6.4a and 6.4b show histograms of the motion magnitudes for the left and right lungs, respectively. In each figure, the uncompensated motion is tabulated as are the model residual errors. Ideally, the model residual errors would all be zero, but they were not due, in part, to the simplification of the model that the motion temporal envelope was constant throughout the lungs, and, in part, to image registration errors. As shown by the model residual error, the cardiac motion was modeled to within 1 mm of its actual motion in this slice. The actual maximum motion was four times greater than the residual error. An overall comparison between the cardiac-induced lung tissue motion and the model residual error for the 10 healthy subjects is shown in Figure 6.5, highlighting the reduction in un-modeled motion. To quantify the accuracy of the model in describing cardiac-induced lung tissue motion, the average relative error for increasing motion envelopes was calculated. The results of this method are shown in Table 6.2 and Table 6.3. Table 6.2 reports the summary of the model’s average absolute and average relative error for the
right and left lungs over various tissue trajectory motion envelopes. Table 6.3 reports the average cardiac-induced motion and the model residual error for the right and left lungs.

\( ||\gamma|| \) was found to vary smoothly throughout the lung. Figure 6.6 shows a typical example of the \( ||\gamma|| \) for a SA view of the left lung. The cardiac-induced lung tissue motion was observed to be greater than 1 mm for 15.5% of the voxels analyzed in this study. These voxels were almost exclusively located in lung regions close to the heart. A rapid decrease in the magnitude of the cardiac-induced lung tissue motion was observed outside of this region. Based on an Ansari – Bradley test, the results for the cardiac-induced lung tissue motion (\( p<0.01 \)), \( ||\gamma|| \) (\( p<0.04 \)), and the model residual error (\( p<0.01 \)) were found to follow an exponential distribution.

Based on the AIC analysis, a 9th order polynomial was found to be the lowest order required to describe the magnitude of lung tissue displacement in each cardiac frame for each voxel. The behavior of \( h \) over the lung for each subject was similar in the right and left lung individually for the ten healthy volunteers. Figure 6.7 shows the behavior of \( h \) over the cardiac cycle for the right and left lungs for the ten healthy subjects.

**Discussion**

This manuscript has proposed a new term for the 5D breathing motion model to account for cardiac-induced lung tissue motion. The cardiac-induced lung tissue motion term followed the form of the other terms in the 5D breathing motion model. The results have shown the potential of the new term to model the cardiac-induced lung tissue motion to within 1 mm. A cardiac cycle varying time scalar quantity, \( h \), scaled the magnitude of \( \gamma \) according to the cardiac phase. To build the model, a deformable image registration algorithm was applied to cardiac
gated planar MR images of the thorax anatomy acquired during breath-hold maneuvers. The maximum displacement of lung tissue caused by the cardiac cycle was observed to be 17.6 mm. This occurred in the region of the lung that was close to the heart – lung boundary. The majority (84.5%) of the imaged lung tissues had less than 1 mm of cardiac-induced motion.

The behavior of $h$ for the right lung was slightly different than the behavior of $h$ in the left lung. The maximum cardiac-induced lung tissue motion occurred at the 9 – 10th cardiac frames for both lungs, which approximately corresponded with the end-systolic phase of the cardiac cycle. The definition of $h$ mirrors the periodic nature of the cardiac cycle, which would permit $h$ to synchronize with another time varying cardiac signal, the ECG. Given this scalar surrogate input $h$, it would be possible to predict the internal motion of lung tissue during the cardiac cycle by scaling $\gamma$, the lung tissue specific response to the cardiac cycle.

Inter-subject variability of $h$ was greater in the right lung than the left lung for both absolute and relative errors. This could be explained by considering the portions of the heart that abut the right and left lungs. For the left lung, the myocardium primarily abuts the lung tissue. These muscles force the ejection of blood from the heart, which causes the greatest lung tissue displacement during the cardiac cycle. The right lung primarily abuts the descending aorta due to the presence of the liver, which limits the surface interaction between the myocardium and the right lung.

The results of this study have an impact on the modeling of lung tissue motion, in particular the modeling of hysteresis motion. In a recent publication, we characterized the distribution of hysteresis during free breathing. The relative amount of hysteresis motion was found to be 8 – 18% of the volume filling component of motion throughout the lung. For
example, consider a lung tissue voxel with a tissue displacement of 20 mm. The hysteresis component of this motion would be between 1.6 – 3.6 mm, encompassing the range of cardiac-induced motion. Cardiac-induced lung tissue motion could degrade the accuracy of the model in predicting hysteresis motion near the heart. The model residual error was much less than 1 mm on average for tissues at all cardiac motion envelopes. This cardiac-induced motion modeling accuracy is expected increase the accuracy of the previously developed 5D breathing motion model for tissues lying near the heart.

**Conclusion**

Cardiac-induced lung tissue motion can be corrected to within 1 mm using the proposed model. The model had a complex time-domain term (a 9th-order polynomial) and a simple spatial domain term (a 3-dimensional vector) to minimize the possibility of the cardiac term inadvertently modeling breathing motion. A future study will examine the impact of the term in breathing motion modeling, especially in regions near the heart.
Figure 6.1: Coordinate system for the cardiac-induced lung motion model.
Figure 6.2: Figure 6.2a shows an overlay example of the reference cardiac frame image with a randomly selected cardiac frame. In Figure 6.2b, the randomly selected cardiac frame warped by the calculated deformation vectors overlaid with the reference cardiac frame is shown. The pixels in red highlight a discrepancy between the reference and randomly selected cardiac frames.
Figure 6.3: The uncompensated cardiac-induced lung tissue motion is shown for a SA view of the left lung (a) and right lung (b). The corresponding model residual error is shown for the left lung (c) and the right lung (d).
Figure 6.4: A sample distribution comparison between the uncompensated cardiac-induced lung tissue motion $|\vec{X}|$ and the model residual error $|\vec{X} - \gamma h|$ for the left lung (a) and the right lung (b) shown in Figure 6.3.
Figure 6.5: Cumulative histogram comparison between the cardiac-induced lung tissue motion and the model residual error for all voxels in the right (a) and left (b) lungs.
Figure 6.6: A typical example of $||\tilde{\gamma}||$ for a SA view of the left lung. The color scale is in units of mm.
Figure 6.7: \( h \) curves for the right (a) and left (b) lungs for the 10 subjects.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{X}$</td>
<td>Lung tissue position</td>
</tr>
<tr>
<td>$\bar{X}_0$</td>
<td>Initial lung tissue position</td>
</tr>
<tr>
<td>$\bar{a}$</td>
<td>Lung tissue specific response to volume filling</td>
</tr>
<tr>
<td>$v$</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>$\bar{\beta}$</td>
<td>Lung tissue specific response to hysteresis</td>
</tr>
<tr>
<td>$f$</td>
<td>Airflow</td>
</tr>
<tr>
<td>$\bar{c}$</td>
<td>Cardiac-induced lung motion term</td>
</tr>
<tr>
<td>$\bar{y}$</td>
<td>Lung tissue specific response to the cardiac motion</td>
</tr>
<tr>
<td>$h$</td>
<td>Lung tissue response to the cardiac cycle</td>
</tr>
<tr>
<td>$c$</td>
<td>Cardiac phase</td>
</tr>
<tr>
<td>$(\bar{u}, \bar{v}, \bar{w})$</td>
<td>Deformation vectors</td>
</tr>
<tr>
<td>$(\bar{i}, \bar{j}, \bar{k})$</td>
<td>Cartesian coordinate system of $\bar{y}$</td>
</tr>
<tr>
<td>$(\theta_x, \theta_y, \theta_z)$</td>
<td>Cartesian coordinate system angles of $\bar{y}$</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criteria</td>
</tr>
<tr>
<td>$k$</td>
<td>Number of parameters in $h$</td>
</tr>
<tr>
<td>$T$</td>
<td>Total number of cardiac frames in a single cardiac cycle</td>
</tr>
<tr>
<td>$L$</td>
<td>Maximum likelihood</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>Variance at a given cardiac frame</td>
</tr>
<tr>
<td>$h^m_{\text{fit}}$</td>
<td>$h$ value from the polynomial fit at a given cardiac frame</td>
</tr>
<tr>
<td>$h^m_{\text{fit}}$</td>
<td>$h$ value at the a given cardiac frame</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>Chi-squared</td>
</tr>
<tr>
<td>$A$</td>
<td>constant under the condition of consistent measurement data</td>
</tr>
<tr>
<td>$s$</td>
<td>Subject</td>
</tr>
<tr>
<td>$n$</td>
<td>Number of voxels</td>
</tr>
<tr>
<td>$j$</td>
<td>Number of coefficients</td>
</tr>
<tr>
<td>$m$</td>
<td>Polynomial coefficient</td>
</tr>
</tbody>
</table>

Table 6.1: Table of variables introduced in this chapter.
<table>
<thead>
<tr>
<th>Motion Envelope</th>
<th>Left Lung Average Absolute Error</th>
<th>Left Lung Relative Error</th>
<th>Right Lung Average Absolute Error</th>
<th>Right Lung Relative Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 – 1 mm</td>
<td>0.32 ± 0.10 mm</td>
<td>63.5 ± 40.0%</td>
<td>0.45 ± 0.20 mm</td>
<td>86.7 ± 75.2%</td>
</tr>
<tr>
<td>1 – 2 mm</td>
<td>0.35 ± 0.12 mm</td>
<td>27.6 ± 7.1%</td>
<td>0.53 ± 0.28 mm</td>
<td>40.0 ± 16.0%</td>
</tr>
<tr>
<td>2 – 3 mm</td>
<td>0.35 ± 0.13 mm</td>
<td>15.0 ± 2.2%</td>
<td>0.58 ± 0.34 mm</td>
<td>24.6 ± 6.0%</td>
</tr>
<tr>
<td>3 – 4 mm</td>
<td>0.36 ± 0.13 mm</td>
<td>10.6 ± 1.1%</td>
<td>0.61 ± 0.38 mm</td>
<td>18.0 ± 3.2%</td>
</tr>
<tr>
<td>4 – 5 mm</td>
<td>0.37 ± 0.14 mm</td>
<td>8.4 ± 0.7%</td>
<td>0.61 ± 0.37 mm</td>
<td>13.7 ± 1.9%</td>
</tr>
<tr>
<td>5 – 6 mm</td>
<td>0.37 ± 0.14 mm</td>
<td>6.9 ± 0.4%</td>
<td>0.58 ± 0.33 mm</td>
<td>10.6 ± 1.1%</td>
</tr>
<tr>
<td>6 – 7 mm</td>
<td>0.38 ± 0.14 mm</td>
<td>5.9 ± 0.4%</td>
<td>0.57 ± 0.33 mm</td>
<td>8.9 ± 0.8%</td>
</tr>
<tr>
<td>7 – 8 mm</td>
<td>0.39 ± 0.15 mm</td>
<td>5.3 ± 0.3%</td>
<td>0.56 ± 0.32 mm</td>
<td>7.5 ± 0.6%</td>
</tr>
<tr>
<td>8 – 9 mm</td>
<td>0.40 ± 0.16 mm</td>
<td>4.7 ± 0.2%</td>
<td>0.55 ± 0.30 mm</td>
<td>6.5 ± 0.4%</td>
</tr>
<tr>
<td>9 – 10 mm</td>
<td>0.40 ± 0.16 mm</td>
<td>4.3 ± 0.2%</td>
<td>0.56 ± 0.31 mm</td>
<td>5.9 ± 0.4%</td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>0.43 ± 0.18 mm</td>
<td>3.5 ± 0.1%</td>
<td>0.60 ± 0.36 mm</td>
<td>4.6 ± 0.2%</td>
</tr>
</tbody>
</table>

Table 6.2: Summary of the average absolute error and average relative error for increasing cardiac-induced lung motion envelopes.
Table 6.3: Summary of average cardiac-induced lung tissue motion and average model residual error for the right and left lungs over all subjects in this study.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Average Cardiac Induced Motion, Left Lung</th>
<th>Average Residual Error Left Lung</th>
<th>Average Cardiac Induced Motion, Right Lung</th>
<th>Average Residual Error Right Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.69 ± 0.47 mm</td>
<td>0.21 ± 0.04 mm</td>
<td>0.80 ± 0.64 mm</td>
<td>0.26 ± 0.07 mm</td>
</tr>
<tr>
<td>2</td>
<td>0.75 ± 0.56 mm</td>
<td>0.23 ± 0.05 mm</td>
<td>0.69 ± 0.48 mm</td>
<td>0.31 ± 0.09 mm</td>
</tr>
<tr>
<td>3</td>
<td>0.67 ± 0.45 mm</td>
<td>0.23 ± 0.05 mm</td>
<td>0.68 ± 0.46 mm</td>
<td>0.28 ± 0.08 mm</td>
</tr>
<tr>
<td>4</td>
<td>0.66 ± 0.43 mm</td>
<td>0.20 ± 0.04 mm</td>
<td>0.65 ± 0.42 mm</td>
<td>0.23 ± 0.05 mm</td>
</tr>
<tr>
<td>5</td>
<td>0.83 ± 0.69 mm</td>
<td>0.43 ± 0.18 mm</td>
<td>0.72 ± 0.52 mm</td>
<td>0.27 ± 0.07 mm</td>
</tr>
<tr>
<td>6</td>
<td>1.00 ± 0.99 mm</td>
<td>0.31 ± 0.10 mm</td>
<td>1.17 ± 1.36 mm</td>
<td>0.48 ± 0.23 mm</td>
</tr>
<tr>
<td>7</td>
<td>1.01 ± 1.02 mm</td>
<td>0.33 ± 0.11 mm</td>
<td>1.18 ± 1.40 mm</td>
<td>0.54 ± 0.29 mm</td>
</tr>
<tr>
<td>8</td>
<td>0.63 ± 0.40 mm</td>
<td>0.23 ± 0.05 mm</td>
<td>0.60 ± 0.36 mm</td>
<td>0.25 ± 0.06 mm</td>
</tr>
<tr>
<td>9</td>
<td>1.03 ± 1.07 mm</td>
<td>0.38 ± 0.15 mm</td>
<td>1.42 ± 2.02 mm</td>
<td>0.70 ± 0.50 mm</td>
</tr>
<tr>
<td>10</td>
<td>1.07 ± 1.14 mm</td>
<td>0.39 ± 0.15 mm</td>
<td>1.58 ± 2.51 mm</td>
<td>0.67 ± 0.44 mm</td>
</tr>
</tbody>
</table>
Chapter 7: Conclusions and Future Work

The purpose of this chapter is to provide a review of the work discussed in this dissertation and to suggest further studies. The introduction chapter discussed the development of the novel 5D breathing motion model and the initial work done to demonstrate the biomechanical properties of the model parameters. The 5D breathing motion model is a unique description of lung tissue trajectories that did not have an implicit dependence on time. The model was shown to be a highly accurate predictor of lung tissue motion during free breathing with low discrepancy. The scope of this dissertation was to propose and validate novel algorithms and protocols for the analysis of motion information in 4DCT. This dissertation continues the development of the 5D breathing motion model to create a comprehensive lung tissue motion model.

Chapters 2-4 used the physiologic nature of the 5D breathing motion model to analyze motion information in 4DCT. Chapter 2 demonstrated the relationship between the geometric expansion of the torso and the tidal volume can be applied to 4DCT images. It proposed the ratio of the thorax-to-abdomen expansion to be approximately 0.32±0.24. This can be directly used in breathing motion studies that utilize body surface expansion as a surrogate for breathing motion modeling. In particular, this work would be of interest for optical camera tracking of the torso surface area.

Chapter 3 investigated the breathing patterns of radiation therapy patients. This study included 50 lung cancer and non-lung cancer patients. Three breathing patterns were observed for the patient cohort and were classified based on the relative amount of time the individual spent in a particular respiratory phase. Type 1 patients spent more time at maximum exhalation compared to any other respiratory phase and constituted 68% of the patient cohort. Type 2
patients spent an equal amount of time at inhalation and exhalation. This was indicative of forced breathing and constituted 26% of the patient cohort. Type 3 patients displayed a chaotic breathing pattern and were in the minority of the patient cohort. This work can be directly applied to optimizing the efficiency of linear accelerator gating. By knowing the breathing type classification of the patient, it may be possible to optimize the gating window to decrease the radiation therapy treatment time.

Chapter 4 highlighted a major benefit of the 5D breathing motion model, demonstrating its ability to characterize complex breathing motions that would otherwise be impossible due to breathing irregularities. The study characterized the relative amount of hysteresis present in lung tissue trajectories. Due to breathing irregularities, a single hysteresis value does not exist. To overcome this limitation, a characteristic breath was defined. The characteristic breath was a single breath that was highly representative of the physical characteristics of the breathing pattern during the scanning session. The characteristic breath provided tidal volume and airflow values for the 5D breathing motion model to create a closed loop trajectory that was highly representative of the actual lung tissue trajectory during the scanning session. The relative amount of hysteresis was found by building a bounding box around the ellipsoidal trajectory and taking the ratio of the width to the height of this box. The analysis found that the relative amount of hysteresis varied between 8-18% of the volume filling component of lung tissue motion. The result demonstrated the amount of additional discrepancy that would be expected for simplistic breathing motion models that do not account for lung tissue hysteresis.

Chapter 5 proposed the use of an ARMA model to predict respiratory phase. The model was developed and optimized for surrogate respiratory traces with an AIC optimization algorithm. The study demonstrated the accuracy of the ARMA model in predicting two difficult
phases of respiration, maximum inhalation and maximum exhalation, for prediction time steps as large as 0.3 s. This would allow the algorithm to predict respiratory phases with high accuracy for 4DCT simulations. The ARMA model prediction was compared to a commercially available prediction model and was found to be significantly better at predicting the time of maximum inhalation and maximum exhalation. The ARMA model has an order of magnitude less error compared to the commercial algorithm for maximum inhalation prediction and two orders of magnitude improvement in error for maximum exhalation prediction. This study demonstrated the feasibility of prospective 4DCT scanning that would reduce the dose delivered to the patient by eliminating the need for redundant scanning of the same anatomical region to account for breathing irregularities.

Chapter 6 introduced a new term for the 5D breathing motion model that accounts for cardiac induced lung tissue motion. In order to be consistent with the 5D breathing motion model, the cardiac induced lung tissue term was expressed as $\gamma h$, where $\gamma$ was a vector that described the cardiac induced lung tissue motion and $h$ was the time dependence of the cardiac induced lung tissue motion. The maximum displacement of lung tissue caused by the cardiac motion was found to be in excess of 4 mm in the region of the lung that was close to the heart-lung boundary. The cardiac induced lung tissue motion term reduced the un-modeled motion by a factor of 2. This addition will decrease the discrepancy of the 5D breathing motion model and will create a comprehensive lung tissue motion model that accounts for more major forces driving lung tissue motion.

**Future Work**

The future direction of the work presented in this dissertation can be seen in the creation of a novel scanning method for 4DCT. Currently, 4DCT is acquired using either a low-pitch
helical protocol\cite{16} or a ciné acquisition protocol\cite{179} performed with breathing surrogate measurements to retrospectively assign a breathing phase to each image. The challenge in implementing both of these techniques is the irregularity of respiration in radiotherapy patients. This causes the 4DCT images to have serious artifacts that limit the use of 4DCT in treatment planning. A new 4DCT protocol that reduces image artifacts, reduces image noise, and provides accurate Hounsfield Units is desirable. Taking advantage of fast gantry rotation periods, fast couch speeds, and accurate synchronization, whole lung volumes were acquired in less than 2.5 seconds on a 64 slice CT scanner (Siemens Definition Flash).\cite{167} This protocol replaced the ciné acquisition protocol that provided the patient data for this dissertation. The new protocol improved the data collection technique by removing motion artifacts and couch position abutment artifacts from the images used for developing the 5D breathing motion model.\cite{167} Currently there have been 9 patients acquired with this protocol. The results have been promising. Most of the lung displays sub-millimeter discrepancy between the tissue motion and the 5D breathing motion model predictions in this cohort.\cite{167} In lung regions close to the myocardium, the discrepancy was greater due to cardiac-induced lung tissue motion. Noise was reduced in the images by a factor of 5.\cite{167} This dissertation demonstrated the benefit of modeling cardiac induced lung tissue motion, so a new ECG surrogate was added to the data collection protocol to monitor the cardiac phase. The ECG will provide the cardiac phase information required for the cardiac induced lung tissue motion term of the breathing motion model.

A major challenge for the breathing motion model will be the variability of the model parameters over time. In order to study the variability of the model parameters, each patient must be imaged multiple times over the course of radiation therapy. A major limiting factor that
prohibits multiple data collection sessions has been the dose delivered for each session. A method to reduce the dose delivered in the scanning sessions has been demonstrated in the use of the ARMA model to predict respiratory phase. The new protocol might be able to take advantage of the ARMA model by predicting respiratory phase to prospectively trigger the CT scanner as discussed in Chapter 5. The challenge will be scanning the lung rapidly to effectively collect a volumetric lung image at a single volume for all slices. It is hypothesized that 5 scans would be sufficient to generate the 5D breathing motion model with this protocol.\textsuperscript{[167]} The ARMA model would function as a means to predict the respiratory phase at the start of each scan. Retrospective analysis of the acquired breathing phases throughout the lung volume during the scan will determine if sufficient data has been collected for accurately building the 5D breathing motion model. The work from Chapter 5 could also be expanded by comparing the ARMA model against other time series prediction models. Expanding the prediction algorithm to predict the respiratory behavior over a single scan (2.5 seconds) would be useful for reducing the dose to the patients by reducing the number of scans needed to build the 5D breathing motion model if the prediction is accurate over the scanning window.

The work presented in Chapters 2-4 will have important ramifications on simplistic breathing motion models that rely on assumptions to reduce the complexity of lung tissue motion. Simplistic models are required for quick motion predictions during therapy for tumor tracking and linear accelerator gating or field shaping. The work discussed in Chapter 2 proposes a fundamental relationship between the geometric expansion of the thorax and the abdomen that can be used for breathing motion modeling and breathing motion studies. The efficiency of linear accelerator gating can be enhanced by the work presented in Chapter 3. Finally, Chapter 4 demonstrated that the relative amount of hysteresis present in lung tissue
trajectory patterns varies between 8-18% of the volume filling component of lung tissue motion. This provides an estimate of discrepancy for lung tissue motion models that do not model the hysteresis motion in lung tissue trajectories. The characteristic breath defined in Chapter 3 can be used to provide repeatable and physiologic breathing traces for breathing motion studies using phantoms. These three studies have the potential to be applied directly in breathing motion studies for clinical use.
References


98. Malinowski, K., et al., Development of the 4D Phantom for Patient-Specific, End-to-End Radiation Therapy QA, in SPIE Medical Imaging Conference. 2007: San Diego, CA.


