Incorporating Pathology-Induced Heterogeneities in a Patient-Specific Biomechanical Model of the Lung for Accurate Tumor Motion Estimation*

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***Abstract*—Radiation therapy (RT) is an important component of treatment for lung cancer. However, the accuracy of this method can be affected by the complex respiratory motion/deformation of the target tumor during treatment. To improve the accuracy of RT, patient-specific biomechanical models of the lung have been proposed for estimating the tumor's respiratory motion/deformation. Chronic obstructive pulmonary disease (COPD) has a high incidence among lung cancer patients and is associated with heterogeneous destruction of lung parenchyma. This key heterogeneity element, however, has not been incorporated in lung biomechanical models developed in previous studies. In this work, we have developed a physiologically and patho-physiologically realistic lung biomechanical model that accounts for lung tissue heterogeneity. Four-dimensional computed tomography (4DCT) images were used to build a patient-specific finite element (FE) model of the lung. Image information was used to identify and incorporate inhomogeneities within the model. Mechanical properties of normal and diseased regions in the lung and the transpulmonary pressure driving the respiratory motion were estimated using an optimization algorithm that maximizes the similarity between the actual and simulated tumor and lung image data. Results from this proof of concept study on a lung cancer patient indicated improved accuracy of tumor motion estimation when COPD-induced lung tissue heterogeneities were incorporated in the model.**

I. Introduction

Lung cancer is the most common cause of cancer-related death with 1.76 million deaths worldwide in 2018 [1]. Radiation therapy (RT) is part of the standard of care for curative treatment of unresectable early-stage or locally advanced lung cancer [2]. Unfortunately, respirartory tumor motion can lead to inaccuracies in RT with potentially serious adverse effects, including harmful irradiation of normal tissue and insufficient dose to the tumor [3]. Advances in RT delivery, such as intensity modulated RT (IMRT) and volumetric modulated arc therapy (VMAT), together with advances in image-guidance systems have made it possible to deliver highly conformal radiation dose distributions. These advances have ushered in a new paradigm in radiation therapy called stereotactic body radiation therapy (SBRT) where much higher biologically effective doses are delivered. Compared to conventional methods, however, this method requires greater accuracy. To further improve the precision of radiation dose delivery to the moving lung tumors, accurate techniques for intra-fraction tumor localization during respiration are needed. In advanced SBRT techniques, radiographically-detectable fiducials can be implanted in the tumor. The real-time information of fiducial positions detected by stereotactic x-ray cameras can be used to gate the radiation, allowing for more precise delivery of higher radiation dose to the tumor [4]. However, implanting the fiducials is invasive and has the potential for adverse side-effects, rendering this technique unsuitable for certain patients. In addition, this method only provides information on the location of the points within the tumor where the fiducials are placed and cannot capture the real-time shape of the tumor, which may change substantially during respiration [5]. Fiducial markers migration is another possible limitation that can compromise the accuracy of tumor tracking [6]. In search for non-invasive computational methods, Li R. et al. [7] adapted deformable image registration (DIR) in conjunction with simultaneous x-ray imaging to estimate the lung tumor motion and deformation. However, exposure of patients to extra radiation dose of the x-ray imaging in these methods has raised some concerns [8]. The integration of magnetic resonance (MR) to radiation delivery systems (MR-linac) provides the possibility of real-time motion management. However, this is an expensive technology that is not readily available.

The respiratory tumor motion/deformation can be estimated using biomechanics-based computational models [9][10]. Such models are based on physiological mechanisms, potentially rendering this approach more robust and realistic.

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Thus, biomechanical models have the potential to eliminate the need for simultaneous imaging during RT or for invasive markers. An accurate patient-specific biomechanical model of the lung, which considers tissue heterogeneity, can improve the accuracy of the real-time tumor tracking methods proposed previously.

Patient-specific lung biomechanical models that use the thoracic image data to extract the lung's geometry and boundary conditions have previously been proposed [9][11][12]. Several studies investigated how model accuracy is affected by the model parameters, including the mechanical properties [13][14] and boundary conditions [15]. In a number of recent studies, finite element (FE)-based biomechanical models were used in conjunction with DIR methods to predict the deformation field of the lung in a respiratory cycle [11][16][17]. Our group proposed a hybrid motion model for real-time estimation of tumor location/deformation [18]. The proposed method translates the chest surface motion data obtained by optical tracking markers to the tumor location/shape, using the lung biomechanical model. In this model, the lung tissue was assumed to be homogeneous; however, more than 60% of lung cancer patients suffer from chronic obstructive pulmonary disease (COPD) [19]. COPD is a heterogeneous disease, characterized by multiple phenotypes including small airways disease (SAD) and parenchymal destruction (emphysema) that cause changes in the structure and mechanical properties of the affected lung tissue [20][21]. Despite the relevance of COPD among lung cancer patients and the importance of tissue mechanical properties for achieving an accurate biomechanical model, to our knowledge, models developed previously do not account for tissue heterogeneity induced by COPD. In addition to providing a better understanding of pathophysiological mechanisms involved in the lung, a biomechanical model of the lung that accounts for local changes in tissue mechanical properties is expected to produce a more realistic motion estimation. For this purpose, we developed a heterogeneous lung biomechanical model that can be used for accurate respiratory tumor motion/deformation estimation as well as lung image registration.

II. Materials and Methods

This research was performed in accordance with the institutional research ethics board approval. A clinical 4DCT respiratory image sequence was chosen from the FLAIR trial [3]. Scans were acquired from a lung cancer patient who was scheduled for external beam RT. The patient was scanned using a 16-slice Philips Brilliance Big Bore CT scanner (Philips Medical Systems, Cleveland, USA) operating in helical mode. The scan used 120 kVp (kV peak) and 400 mAs/slice for tube potential and current, respectively. The intra-slice pixel spacing was 1.1 mm × 1.1 mm while the slice thickness was 3 mm. The gross tumor volume was 5.7 cm^3 on the end-exhale (EE) image and its location was in the right lower lobe as illustrated in Fig. 1.

To develop a patient-specific biomechanical model, lung geometry, tissue mechanical properties, loadings, and boundary conditions are required. The geometry of the lung was obtained from the CT image at EE phase using a semi-automatic region growing segmentation technique, followed by opening and closing operations to smooth the segmented

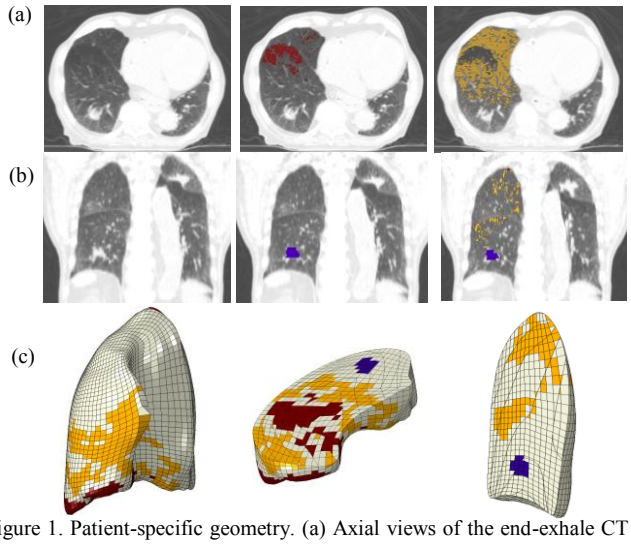

Figure 1. Patient-specific geometry. (a) Axial views of the end-exhale CT of 3 slices, showing emphysema regions in red (middle) and SAD in yellow (right). (b) Coronal views of the end-exhale CT, showing the tumor in blue (middle) and its proximity to diseased areas (right). (c) FE mesh of the right lung (left), an axial (middle) and coronal (right) cross-section of the mesh. Yellow, red and blue show SAD, emphysema, and tumor regions, respectively.

lung surface. A three-dimensional (3D) model of the lung was generated from the segmented lung volume, using the open-source 3DSlicer software package [22]. The IA-FEMesh software package (MIMX, the University of Iowa, Iowa City, IA, USA) was then used to generate an FE mesh of the lung using 8-noded hexahedral elements (Fig. 1c).

To model the COPD-induced heterogeneities within the lung parenchyma, the extents of COPD phenotypes were determined using the CT data. A well-accepted attenuation-based method was used to quantify the COPD phenotypes using the 4DCT data. Regions in the end-inhale CT volume with attenuation values lower than -950 Hounsfield Units (HU) denote emphysema and regions in the end-exhale CT volume with attenuation values lower than -856 HU represent air trapping. Regions with SAD were determined in the end-exhale CT data as air trapping areas that are not emphysematous [23]. A deformable image registration was used to find the corresponding emphysematous voxels in the end-exhale volume. The percentages of the lung volume at EE affected by SAD and emphysema were determined at 18.9% and 5.0%, respectively. The diseased areas were incorporated in the FE model with different mechanical properties (Fig. 1c).

The lung parenchyma was classified into 4 sub-types: healthy, emphysematous, regions affected by SAD, and gross disease (tumor). The Yeoh hyper-elastic model was used to describe lung tissue elasticity behavior. The Yeoh hyperelasticity parameters for healthy sub-type were found based on experimental data available in the literature [24]. The hyperelasticity parameters for diseased lung tissues (i.e. emphysema and SAD) were determined using optimization. The details of the optimization framework are described later in the methods. Similar to the approach proposed previously by our group [14], we took into account changes in the incompressibility of the lung tissue due to changes in the air volume within the lung parenchyma during the respiration cycle. As such, the compressibility of the lung parenchyma in

the model (all sub-types, excluding the tumor) was considered a temporally variable parameter. The tumor was modeled as a linear elastic (Young's modulus = 10 kPa) and nearly incompressible material with a Poisson ratio of 0.49.

The loading and boundary conditions of the model were defined based on the respiration physiology. The lung motion/deformation during both inhalation and exhalation is a passive process that is driven by changes in trans-pulmonary pressure and diaphragm contraction and relaxation, respectively. Accordingly, for the former, the loading of the biomechanical model was defined in terms of the trans-pulmonary pressure required to expand the relaxed state of the lungs at EE phase to the target phases of respiration. A spatially variable pressure was applied with an anterior to posterior gradient wherein its maximum amplitude was optimized for each respiration phase. To account for loading pertaining to the diaphragm contraction, the diaphragm surface displacement was estimated through a free-form deformable image registration and was assigned as prescribed displacement boundary conditions to the bottom surface of the lung. Some regions of the lung have anatomically restricted motion. Therefore, in addition to displacement boundary conditions, fixed boundary conditions were extracted from the 4DCT data using an automatic algorithm.

As indicated earlier, an optimization framework (Fig. 2) was developed to find the values of the unknown model parameters, *i.e.* the pressure amplitude, the hyperelasticity parameters of the pathological regions of the lung, and the incompressibility parameter. The lung and tumor volumes were segmented from CT data for all phases. In the first iteration, the FE analysis was carried out with initial values of the unknown parameters, and the results were passed to the cost function shown in (1). A simplex optimization algorithm was used to find the optimal parameters that maximize the accuracy of tumor motion estimation by minimizing the following hybrid cost function [25]:

$$f_C\left(P,\ C_{Emph}, C_{SAD}, D\right) = \alpha \times H(T_{sim}, T_t) + \beta / Dice(T_{sim}, T_t) + \gamma / MI(L_{sim}, L_t), \quad (1)$$

where each term in this equation is described below. The cost function incorporated the distance and similarity measures between the segmented images of the tumor and lung from 4DCT at target phase and their FE simulated counterparts. Equation (1) describes the cost function where T_{sim} and T_t represent the FE simulated tumor geometry and its segmented counterpart at the target phase, respectively. Similarly, L_{sim} and L_t represent the FE simulated deformed lung geometry and its segmented counterpart at the target phase, respectively. Also, H, $Dice$, and MI represent the tumor's Hausdorff surface to surface distance function, it's Dice similarity measure and mutual information (MI) measure, respectively. α, β, and γ are constants used as weight factors, and were chosen based on the importance, and the range of the variations of each measure. Considering that the main purpose of this study is tumor motion/deformation estimation, we chose $\alpha = \beta = 2\gamma$. The optimization parameters included the pressure amplitude (P), the hyperelasticity properties of diseased tissue sub-types (C_{Emph}, C_{SAD}), and compressibility parameter (D). The final optimized parameters were then used in the biomechanical model for motion estimation of the tumor and the lung.

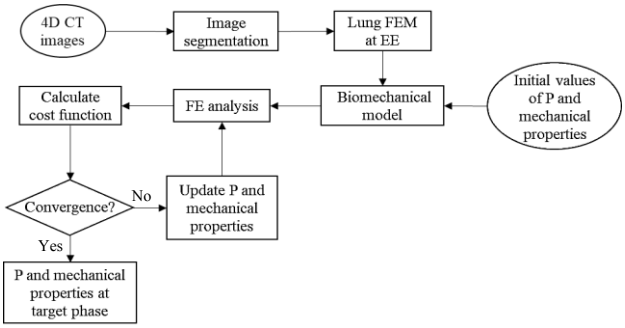

Figure 2. Block-diagram of the proposed optimization algorithm.

The tumor motion/deformation was modeled for 10 respiratory phases in a 4DCT sequence using the heterogeneous lung biomechanical model, incorporating the changes in the mechanical properties of the lung induced by COPD phenotypes. A homogeneous model, consisting of only the lung parenchyma and the tumor was also developed to investigate the impact of incorporating the COPD-induced heterogeneities on the model. These two models were compared in terms of accuracy of tumor motion/deformation estimation (using measures of similarity and distance), as well as their functionality as an image registration algorithm for lung 4DCT images.

III. Results

Measures of similarity, including the Dice similarity coefficient, true positive rate (TPR), and volume similarity (VS), as well as surface-to-surface distance, were employed to quantify the accuracy of the tumor motion/deformation estimation. Table I presents results of the above measures obtained with the homogeneous and heterogeneous models. The average values of similarity measures indicate that both models can estimate the tumor motion/deformation with high accuracy, with the heterogeneous model performance being superior denoted by improved average accuracy and lower standard deviation.

TABLE I. Measures of Similarity and Distance Between Actual and Simulated Tumors

	Homogeneous	**Heterogeneous**
Dice	0.794 ± 0.280	0.882 ± 0.031
TPR	0.806 ± 0.285	0.895 ±0.041
VS	0.912 ± 0.059	1.013 ± 0.060
Surface distance (mm)	0.627 ± 0.129	0.594 ± 0.121

The performance of the biomechanical model-based image registration was assessed by identifying 35 landmarks throughout the lung volume using bifurcation points and computing the mean landmarks error (MLE). The landmarks were categorized into three sets, including those reasonably close to the pathological volumes, reasonably close to the tumor, and embedded in healthy volume. The three sets were then used to calculate MLE_{patho}, MLE_{tumor}, and $MLE_{healthy}$, respectively. These values are reported in Table II. The MLE values demonstrate the local impact of incorporating the heterogeneities on registration accuracy.

TABLE II. MLE BEFORE REGISTRATION, AND AFTER HOMOGENEOUS AND HETEROGENEOUS MODEL-BASED REGISTRATION

	Before Registration (mm)	After Registration	
		Homogeneous (mm)	*Heterogeneous (mm)*
$MLE_{Overall}$ (35)	6.64 ± 4.28	1.55 ± 0.62	1.27 ± 0.44
MLE_{Patho} (10)	6.32 ± 4.42	1.72 ± 0.71	1.22 ±0.41
MLE_{tumor} (8)	4.66 ± 1.92	1.63 ± 0.84	1.28 ± 0.66
$MLE_{healthy}$ (17)	7.76 ± 4.80	1.41 ± 0.43	1.30 ± 0.35

IV. DISCUSSION AND FUTURE WORK

A heterogeneous biomechanical model of the lung was proposed for accurate estimation of respiratory tumor motion/deformation estimation and for improved lung CT image registration. The ability to model the lung tumor motion and deformation can facilitate compensation for inter- and intra-fraction respiratory motions in RT for lung cancer patients. The proposed FE-based model was developed to improve previously-proposed lung biomechanical models, in terms of patho-physiological realism and accuracy of tumor motion estimation and lung CT image registration.

As far as the tumor deformation is concerned, incorporating the COPD-induced changes in the lung structure and mechanical properties proved advantageous as demonstrated by improved measures of accuracy (Table II). Concerning the lung image registration, comparing the MLE results indicate that the heterogeneous biomechanical model has the potential to be applied for accurate registration of respiratory image sequences. Although the MLE is reduced in all landmark sets when the heterogeneous model is used, improvements in the registration accuracy were more substantial in landmarks located at the proximity of COPD-affected regions. If confirmed with more cases, this observation may indicate that accounting for regional variations in the mechanical properties is important for achieving higher local registration accuracy. The patient-specific heterogenous biomechanical model proposed in this study requires further validation using a larger cohort of patients with different tumor locations, tumor volumes, and extent of COPD.

To our knowledge, this study proposed for the first time a model for lung and tumor motion/deformation estimation that takes into consideration structural alterations in the lung caused by COPD. The results obtained in this proof-of-concept study are promising, implying a potential of this approach for being adapted to estimate tumor motion and deformation during respiration for more accurate radiation treatment planning.

REFERENCES

[1] "Cancer." [Online]. Available: www.who.int. [Accessed: 04-Feb-2019].

[2] K. S. Albain *et al.*, "Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial," *Lancet*, 2009.

[3] D. A. Hoover *et al.*, "Functional lung avoidance for individualized radiotherapy (FLAIR): Study protocol for a randomized, double-blind clinical trial," *BMC Cancer*, 2014.

[4] R. D. Wiersma, W. Mao, and L. Xing, "Combined kV and MV imaging for real-time tracking of implanted fiducial markers," *Med. Phys.*, 2008.

[5] Y. Ge, R. T. O'Brien, C. C. Shieh, J. T. Booth, and P. J. Keall, "Toward the development of intrafraction tumor deformation tracking using a dynamic multi-leaf collimator," *Med. Phys.*, 2014.

[6] J. C. Hong *et al.*, "Migration of implanted markers for image-guided lung tumor stereotactic ablative radiotherapy," *J. Appl. Clin. Med. Phys.*, 2013.

[7] R. li *et al.*, "WE-C-204B-05: Real-Time Volumetric Image Reconstruction and 3D Tumor Localization Based on a Single X-Ray Projection Image during Lung Cancer Radiotherapy," in *Medical Physics*, 2010.

[8] M. Nakamura *et al.*, "Quantification of the kV X-ray imaging dose during real-time tumor tracking and from three- and four-dimensional cone-beam computed tomography in lung cancer patients using a Monte Carlo simulation," *J. Radiat. Res.*, 2018.

[9] R. Werner, J. Ehrhardt, R. Schmidt, and H. Handels, "Patient-specific finite element modeling of respiratory lung motion using 4D CT image data," *Med. Phys.*, 2009.

[10] B. Fuerst *et al.*, "Patient-specific biomechanical model for the prediction of lung motion from 4-D CT images," *IEEE Trans. Med. Imaging*, 2015.

[11] L. Han, H. Dong, J. R. McClelland, L. Han, D. J. Hawkes, and D. C. Barratt, "A hybrid patient-specific biomechanical model based image registration method for the motion estimation of lungs," *Med. Image Anal.*, 2017.

[12] E. Karami, S. Gaede, T.-Y. Lee, and A. Samani, "A biomechanical approach for in vivo lung tumor motion prediction during external beam radiation therapy," in *Medical Imaging 2015: Image-Guided Procedures, Robotic Interventions, and Modeling*, 2015, p. 94151.

[13] A. Al-Mayah, J. Moseley, M. Velec, and K. Brock, "Effect of friction and material compressibility on deformable modeling of human lung," in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 2008.

[14] Z. Shirzadi, A. Sadeghi-Naini, and A. Samani, "Toward in vivo lungs tissue incompressibility characterization for tumor motion modeling in radiation therapy," *Med. Phys.*, 2013.

[15] A. Al-Mayah, J. Moseley, M. Velec, and K. K. Brock, "Sliding characteristic and material compressibility of human lung: Parametric study and verification," *Med. Phys.*, 2009.

[16] N. Samavati, M. Velec, and K. Brock, "A hybrid biomechanical intensity based deformable image registration of lung 4DCT," *Phys. Med. Biol.*, 2015.

[17] M. Li *et al.*, "Modeling lung deformation: A combined deformable image registration method with spatially varying Young's modulus estimates," *Med. Phys.*, 2013.

[18] S. Gaede, T.-Y. Lee, A. Samani, and E. Karami, "A machine learning approach for biomechanics-based tracking of lung tumor during external beam radiation therapy," in *Medical Imaging 2018: Image-Guided Procedures, Robotic Interventions, and Modeling*, 2018.

[19] D. Spyratos, E. Papadaki, S. Lampaki, and T. Kontakiotis, "Chronic obstructive pulmonary disease in patients with lung cancer: prevalence, impact and management challenges," *Lung Cancer (Auckland, N.Z.)*, vol. 8, p. 101—107, 2017.

[20] J. MEAD, I. LINDGREN, and E. A. GAENSLER, "The mechanical properties of the lungs in emphysema.," *J. Clin. Invest.*, vol. 34, no. 7, Part 1, pp. 1005–1016, Jul. 1955.

[21] T. Liu, Y. Wang, J. Ma, D. Li, and Y. Fan, "Effects of changing small airway mechanics and inspiratory flow waveforms on pulmonary ventilation: A modeling study," in *IFMBE Proceedings*, 2015.

[22] "http://www.slicer.org."

[23] C. J. Galbán *et al.*, "Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression," *Nat. Med.*, 2012.

[24] Y. J. Zeng, D. Yager, and Y. C. Fung, "Measurement of the Mechanical Properties of the Human Lung Tissue," *J. Biomech. Eng.*, 1987.

[25] J. C. Lagarias, J. A. Reeds, M. H. Wright, and P. E. Wright, "Convergence Properties of the Nelder--Mead Simplex Method in Low Dimensions," *SIAM J. Optim.*, 1998.