Towards a Dynamic Model of Pulmonary Parenchymal Deformation: Evaluation of Methods for Temporal Reparameterization of Lung Data

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Abstract. We approach the problem of temporal reparameterization of dynamic sequences of lung MR images. In earlier work, we employed capacity-based reparameterization to co-register temporal sequences of 2-D coronal images of the human lungs. Here, we extend that work to the evaluation of a ventilator-acquired 3-D dataset from a normal mouse. Reparameterization according to both deformation and lung volume is evaluated. Both measures provide results that closely approximate normal physiological behavior, as judged from the original data. Our ultimate goal is to be able to characterize normal parenchymal biomechanics over a population of healthy individuals, and to use this statistical model to evaluate lung deformation under various pathological states.

1 Introduction

The lung is a highly elastic organ composed of fibers connecting the large airways, intricate vasculature and pulmonary interstitium. Pathological processes that affect the lung typically alter the normal mechanical properties of lung tissue, and manifest as observable changes in lung morphology and function. Magnetic resonance (MR) imaging and other structural imaging modalities can be used to capture *in vivo* deformation of the lung between sequential images by harnessing the power of non-rigid registration algorithms, [1,2,3,4,5].

One of the challenges in evaluating the respiratory dynamics of multiple individuals lies in achieving temporal correspondence between physiologically similar points of the respiratory cycle. We refer to this process of establishing temporal correspondence as *reparameterization*. Solutions have been proposed that include extending the B-spline framework used to perform pairwise registrations to simultaneous spatio-temporal image matching, as well as applying translation and scaling in the temporal domain as a precursor to non-rigid registration in the spatial domain, [6,7].

We extend the technique of combining *capacity*-based reparameterization with shape and intensity averaging to establish a temporal correlation between sequences of lung images from different individuals, [8]. In earlier 2-D experiments, capacity was defined as the cross-sectional area of both lungs computed from coronal slices, and computed via interactive level-set segmentation, [9]. The

data used in those experiments were acquired from human volunteers instructed to breathe slowly and deeply. Imaging was performed at a regular time interval; however, a consistent volume increment was not guaranteed between successive images in the sequence. One limitation of this study was computing lung capacity from 2-D lung MR images containing both a cross-section of parenchyma and portions of large blood vessels. In addition, there is inherent uncertainty associated with matching anatomy moving perpendicularly to the imaging plane.

In light of these confounding issues, we further investigate the reparameterization problem using 3-D whole-lung data. We evaluate the feasibility of two different interpolation techniques for the purposes of 1) reconstructing physiologically appropriate lung configurations between acquired images, and 2) using these reconstructions to establish temporal correspondences between sequences from different individuals. The latter aim lends itself to the construction of dynamic atlases of the normal lung, which is the ultimate goal of this research. We examine two approaches: direct shape averaging and interpolation of sequential images based on deformation computed within our non-rigid registration framework [10], and volume-based reparameterization via linear interpolation. We evaluate each method by comparing the expected *total* lung capacity (TLC) with the capacity in the reconstructed images. We also evaluate the methods by comparing the expected deformation between anatomies to the achieved deformation after reparameterization.

The goal of reparameterization is to establish a standard *physiologic time* axis between individuals who breathe at different rates and whose lungs undergo unique degrees of deformation. By developing this temporal correspondence between individuals, we can construct a dynamic atlas of normal parenchymal deformation and subsequently evaluate the lung motion of patients against this statistical norm.

2 Methods and Materials

2.1 Murine Data

The dataset used in these experiments was acquired using mechanical ventilation of a normal mouse weighing approximately twenty-six grams. First, tracheal cannulation of the anesthetized mouse was performed. The mouse was then connected to a small animal ventilator (FlexiVent, SCIREQ, Quebec, Canada) and mechanically ventilated at a rate of 120 breaths per minute. Four volumetric MR images were acquired using a 4.7T animal imaging system (Biospec 47/40, Bruker BioSpin, Karlsruhe, Germany) at the following physiologic time points: end-expiration, mid-inspiration, end-inspiration and mid-expiration. The first time point was duplicated to produce a dataset of five time points over a single murine breath (figure 1).

2.2 Method Summary

In these experiments we employ a variational registration algorithm with a linear elastic prior to quantify lung motion captured in serial image sequences, by

Fig. 1. Results of the reparameterization algorithm. Deformation of the murine lungs over one complete, reconstructed respiratory cycle (inspiration followed by expiration). Times are given in normalized units as described in the text. Odd images are original acquisitions, and are labeled with the appropriate physiologic phase of respiration; even images are intermediate images reconstructed from the anatomies at adjacent time points in the cycle.

registering sequential pairs of images I and J and examining the resulting displacement fields, [5]. We impose the linear elastic behavior of the image via a finite element mesh constructed over the domain of I . In related work, the original registration algorithm has been modified to yield the diffeomorphic fluid deformation framework which is assumed in this paper, [10]. The diffeomorphic component requires that the solution to the registration be continuous, differentiable and invertible. When combined with the fluid framework and approached from the Eulerian perspective, the total deformation between fixed image I and moving image J is considered to be a composition of incremental transformations, each of which is diffeomorphic.

First, we perform pairwise registration between consecutive images using our fluid registration algorithm. The resulting set of deformation fields, $\{\mathbf{u}_1, \dots, \mathbf{u}_4\}$, reveals not only the motion of the lungs between successive images, but also the change in volume between each image pair through the *total Jacobian* of the field, $\mathcal{J} = \int |J(\mathbf{u}_i)| d\mathbf{x}$ (here, J is the Jacobian matrix and Ω is the domain of the lung segmentation). By construction, A_{i+1} , the capacity of the lungs at the next time, is equal to $\int_{\Omega} |J(\mathbf{u}_i)| d\mathbf{x}$.

Lung volumes are estimated via segmentation with the region competition mode of ITK-SNAP, [9], an open-source, level set implementation of 3-D geodesic active snake segmentation, [11]. The segmentations are not post-processed in any way; the trachea and large vessels traveling between the heart and lungs are omitted from the calculation of lung tissue volumes. The large pulmonary arteries and veins appear as regions of high intensity within the pulmonary parenchyma, and are consistently excluded from the segmentations.

Total lung capacity is estimated at each of the five time points during the respiratory cycle, and shown in figure 2a. The plot demonstrates that the volume of the murine lungs follows a parabolic path during respiration, which is in

Fig. 2. (left) Trend of TLC during a single ventilator-dependent breath in a healthy mouse. (right) Comparison of normalized TLC in original image data to volume- and deformation-based interpolated images over the same breath. Note that the reconstructed anatomies bear TLC values that fall along the expected physiologic trend.

agreement with both the input to the ventilator as well as the expected pattern of respiration typically observed during tidal (passive) breathing via spirometry, [12]. The capacities computed from the original image data are subsequently used to evaluate the images reconstructed with our interpolation techniques.

2.3 Deformation-Based Reparameterization

We employ a shape and intensity averaging algorithm that computes an average anatomy by performing a simultaneous, symmetric registration of two images I and J , [13]. The registration simultaneously determines the diffeomorphism from I to J and J to I ; the latter simulates a temporal path which can be sampled at specific intervals. The symmetric energy of the pairwise averaging problem is

$$\Pi_{sym}(I, J) = \inf_{\mathbf{v}_1} \inf_{\mathbf{v}_2} \int_0^1 \{ \|\mathbf{v}_1\|_L^2 + \|\mathbf{v}_2\|_L^2 + (\|\mathbf{v}_1\|_L^2 - \|\mathbf{v}_2\|_L^2)^2 + \int_{\Omega} \Pi_{\sim}(I \circ \phi_1(\mathbf{X}), J \circ \phi_2(\mathbf{x})) d\Omega \} dt,$$

where $\mathbf{v}_i$ represents the speed and trajectory of the image voxels as they move through the Eulerian reference frame, $\Pi_{\sim}$ is the contribution of the similarity to the overall objective function, and $\mathbf{X}$ and $\mathbf{x}$ are the coordinate systems of I and J , respectively. Integration of $\mathbf{v}_i$ gives the flow ϕ_i in time, which can be used to map between the coordinate systems of I and J . Specifically, ϕ_1 pulls image I into the space of image J , while ϕ_2 provides the inverse mapping of image J into the space of image I . The symmetric solutions to the registration are given by $I \circ \phi_1$ and $J \circ \phi_2$, and the shape and intensity average of images I and J is represented by $\frac{1}{2}(I \circ \phi_1 + J \circ \phi_2)$. In our experiments, this anatomical mean at time t_j represents the average respiratory deformation between the lung configurations at times t_i and t_{i+1} (where $t_i < t_j < t_{i+1}$).

The effect of this approach is to reparameterize the image sequence by deformation, in order to reconstruct the lungs at intermediate configurations between the originally acquired images. The interpolated images are evaluated by calculating TLC at the intermediate times t_j and comparing them to the observed trend of lung capacity. In addition, the deformation between reconstructed lung configurations is also evaluated with respect to the deformation between the original anatomy.

2.4 Capacity-Based Reparameterization

Since the deformation between successive images at i and $i + 1$ is small in this ventilator-assisted dataset, we define our capacity-based reparameterization to be a linear scaling of the deformation between successive images. For example, V_j , the reconstructed image between V_i and V_{i+1} (or images I and J , respectively), can be written as

$$V_j = V_{i+\alpha} = \frac{1}{2}(V_i \circ \alpha\phi_1 + V_{i+1} \circ (1 - \alpha)\phi_2),$$

where α represents the desired capacity fraction between the image pair. Setting $\alpha = 0.5$ produces the anatomic configuration with an estimate of the average TLC between the known lung configurations.

2.5 Validation

TLC is computed at each of the five time points in our 3-D image sequence and shown in figure 2. We reconstruct deformation- and capacity-based ($\alpha = 0.5$) anatomic averages between sequential pairs of images (figure 1). The results are evaluated by comparing the capacities A_j of the successive average lung configurations V_j to the trend observed in the original data (figure 2).

In order to effectively validate the physiologic relevance of our two reparameterization schemes, we first generate a synthetic data sequence by densely sampling the inspiratory phase of our original dataset. This sequence of twelve images over the inspiratory phase of respiration is generated by shape interpolation between end-expiratory and end-inspiratory image volumes EE1 and EI, and serves as synthetic data from a second individual (“mouse” B) whose lung deformation we wish to correlate with that of our original individual (mouse A). Furthermore, we compute a third sequence of twelve images between EE1 and EI via volume reparameterization (“mouse” C). Lung capacities for sequences B and C are shown in figure 3a). Since the synthetic data was produced from the original respiratory endpoints, we have a ground-truth estimate against which to evaluate our method. However, since the trends of TLC in sequences B and C are not identical to that in mouse A, we are not artificially imposing a correct outcome by using this approach.

We normalize TLC to $[0, 1]$ such that capacity at end-inspiration becomes 1 and capacity at end-expiration becomes 0. We also normalize imaging time to $[0, 1]$ such that EE1=0, EI=0.5 and EE2=1. This enables us to make meaningful comparisons between individuals whose tidal volumes and breathing times will

Fig. 3. (left) Comparison of normalized TLC from the original data (mouse A) with that from the deformation-based (B) and volume-based (C) interpolations. (right) Comparison of normalized deformation observed in the original data and the deformation- and capacity-based synthetic sequences. The dotted boxes highlight the anatomies with deformation coincident to that at MI and ME in mouse A.

naturally vary within some normal limits. Using the synthetic data, we attempt to reconstruct (via deformation- and volume-reparameterization in mice B and C, respectively) the anatomy that corresponds to the mid-inspiratory anatomic configuration of mouse A. First, we locate the image pair in sequence B whose normalized capacities are adjacent to the desired capacity in mouse A. Then, we compute the deformation-based average of this pair, and evaluate the capacity in this reconstructed image. It may be necessary to compute a set of shape interpolants between the adjacent images in order to find the best match to the target image. Additionally, we compare this deformation-based mean to the volume-based average estimated from the capacities of the two image neighbors in sequence C. This analysis is similarly performed for the mid-expiratory lung configuration in mouse A (figure 3a).

We also evaluate our reparameterization methods based on the expected deformation from a specific respiratory endpoint required to achieve a desired anatomic configuration. In this case, the total deformation over the entire breath is normalized such that 0 represents EE1, 0.5 the deformation required to arrive at EI and 1 the cumulative deformation to return to EE2 (figure 3b). Deformation is computed as the total magnitude of the gradient of the displacement field divided by the size of the image domain. First, we sum the incremental deformation pairwise between the original image volumes in mouse A. Next, we sum the incremental deformation computed pairwise between the synthetic image volumes in sequences B and C. The deformation required to deform the end-expiratory anatomy to the mid-inspiratory and mid-expiratory time points in mouse A is compared to the corresponding deformation in sequences B and C (figure 3b).

3 Results

Figure 2 compares the normalized capacity in the original data to those in the pairwise averages computed by our two interpolation techniques. Both methods

produce virtually identical results, differing by 0.01 in the capacity estimates at normalized times $t = 0.125$ and $t = 0.875$ and by 0.001 in the estimates at $t = 0.375$ and $t = 0.625$. The error between the expected and achieved capacities was approximately 0.007 at $t = 0.125$ and $t = 0.875$ and 0.03 at $t = 0.375$ and $t = 0.625$.

The discrepancy in normalized TLC between the synthetic sequences computed via deformation- and capacity-based interpolation is approximately 0.002-0.03 per interpolant. However, the average configuration between the anatomies adjacent to the mid-inspiratory (open square) and mid-expiratory (open circle) configurations has a capacity within 0.0004 when computed by either method (figure 3a). The expected normalized lung capacity at MI was 0.281, while the reconstructed anatomy at MI had a capacity of 0.294. The computed normalized capacity at ME was 0.252.

Evaluation of both interpolation methods with respect to deformation is summarized in figure 3b. The corresponding mid-inspiratory and mid-expiratory anatomic configurations among sequences A-C are enclosed in the dotted boxes. The error in normalized deformation to arrive at MI is approximately 0.001, while the corresponding error to reach ME is approximately 0.025. The discrepancy between the deformation- and capacity-based approaches is approximately 0.003 at MI and 0.008 at ME. In addition, the closest image pair providing the matching deformation at MI and ME is the same image pair used to compute the deformation- and capacity-based average anatomies based on normalized TLC in figure 3a. This further validates the physiological basis of our approach.

4 Discussion and Future Work

We present an evaluation of two approaches toward the temporal reparameterization of dynamic lung data. Comparable results are achieved using both deformation-based shape and intensity averaging and volume-based linear scaling. The parenchymal deformation in this whole-lung mouse dataset is more uniform compared to that observed in 2-D data used in earlier experiments. In addition, the deformation between successive images is small, since the tidal volume in this animal is only around 0.2 ml. As a result, we plan to evaluate these methods on additional volumetric datasets acquired with non-zero and non-constant settings for positive end-expiratory pressure (PEEP).

Future analysis will also be extended to data acquired with breath-holding, since human imaging is typically not conducted with mechanical ventilation. Application of the techniques presented in this paper is not restricted to data acquired with ventilatory assistance; however, validation of the methods is augmented by the regular pattern of respiration imposed by the ventilator.

The ultimate goal of this research is to use temporal correspondences between individuals to provide comparisons of the biomechanical perturbation of the lung during respiration. Mechanics can be evaluated by computing finite strain over the respiratory cycle, and investigating regional variations in tissue character within as well as between individuals. By establishing temporally

coincident anatomic points between individuals, it will be possible to assess the degree and distribution of strain required for these individuals to arrive at physiologically similar points in their respective respiratory cycles. Furthermore, various pulmonary pathologies are known to affect the mechanical properties of the lung tissue, and these changes can be quantified using the model described. Our work motivates the construction of dynamic atlases of normal lung motion, which will not only provide a statistical representation of normal parenchymal deformation but also a metric against which to evaluate changes introduced by the development and progression of pulmonary diseases.

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