Image Registration of Lung CT Scans for Monitoring Disease Progression

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PhD thesis

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Image Registration of Lung CT Scans for Monitoring Disease Progression

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Submitted: 23/07/2010

To my parents Victor and Tatyana

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Chapter 1

Introduction

A journey of a thousand miles must begin with a single step

— Lao-Tzu

1.1 Chest Computed Tomography

Figure 1.1: Picture of the first medical X-Ray image of a hand. *Reprint from* [1].



Modern computed tomography originated back in November 1895 in the experiments of Wilhelm Conrad Röntgen with an X-ray tube and a fluorescent screen. He discovered, that unknown invisible rays, X-rays, passed through paper and wood and cast a shadow on a fluorescent screen, while it could not travel through metal pieces. When he put his hand into the beam he was surprised to see bones in the casted shadow. Shortly after he photographed his wife, Anna Berthe Röntgen's, hand with the X-Ray beam Figure 1.1 and published a paper on his discovery [1]. The paper made a sensation and spread around the world within few weeks. Already in 1901 he received the Nobel Prize in Physics for his breakthrough discovery.

The impact of the discovery on medical science was colossal, it was the first time, when one could see inside the human (a) An axial slice (b) A coronal slice (c) A sagittal slice

body without direct intervention. Shortly after in 1896, Francis Williams started X-Ray examinations of patients with tuberculosis [2]. Owing to the fact that he had access to the state-of-the-art equipment in the Massachusetts Institute of Technology, he was able to carry out thorough research of tuberculosis using the

Figure 1.2: Hounsfield scale of a CT scan

fluoroscopic examination.



For a long period, projection radiography was one of the most popular techniques for medical imaging. The idea of imaging just a section of an object was pioneered by Allesandro Vallebona back in 1931 [3]. The term *tomogram* refers to the obtained image of a single section or a slice of an object and the method is called tomography. Almost half a century later in 1972 the revolution in medical imaging begun. Godfrey Hounsfield invented computed axial tomography (CAT or simply CT) [4] where a volumetric image of an object was reconstructed from a series of axial tomograms. Since then, computed tomography progressed rapidly from the first CT scanner developed by Godfrey Hounsfield and

applicable only for imaging of small objects to the full body scan in 1976 and the first spiral CT scanner in 1989. Modern CT scanners acquire chest CT scans with high spatial resolution up to 0.5 mm just within several seconds and with the radiation of dozens times smaller than the original CT scanner. An example of a modern chest CT scan is shown in Figure 1.3.

Attenuation coefficient characterizes the decrease of energy of an X-Ray beam

passing through matter. Chest CT scan is a volumetric image where intensity values corresponds to the attenuation coefficient of the matter. A unit of intensity is the Hounsfield Unit (HU). The Hounsfield unit scale is a linear scale of the original attenuation coefficients or the radiodensity. The attenuation coefficient of distilled water under a standard pressure and temperature (0°C, 1 atm) is set to $\mu_{H_2O} = 0$ HU, and the attenuation coefficient of air is set to $\mu_{air} = -1000$ HU. A general value μ HU corresponds to a material with the attenuation coefficient $\frac{\mu - \mu_{H_2O}}{\mu_{H_2O} - \mu_{air}} \times 1000$. The range of Hounsfield Units for human tissues, such as bones, fat, water, blood and muscles is given in Figure 1.2. Typical range of HU for the anatomical structures observed in a lung CT scan is from -1000 HU (corresponds to the attenuation of blood). Air in the lung CT appears dark and blood vessels appear bright as one can see in Figure 1.3.

A modern volumetric lung CT scan is a three dimensional image with typically a sub-millimeter in-plane resolution and slice thickness of about 1 mm. However for several clinical applications such as radiation therapy planning a time series of lung CT scans is acquired during a breathing cycle. The obtained four dimensional image is called 4D-CT or dynamic CT lung scans, and along with the regular lung CT scans, images extracted at different phases of 4D-CT lung scans are used in this thesis.

1.2 Anatomy of Lungs

When an experienced radiologist looks at a lung CT scan in Figure 1.4, he or she immediately recognizes the anatomical structures presented in the image. As a computer scientist, it took me a while before the sagittal, coronal and axial slices formed into a meaningful three dimensional picture of human lungs. The following anatomical lung structures can be identified in chest CT scans:

- Alveolar lung tissue or parenchyma (typically appears as grey homogeneous matter),
- Pulmonary vasculature (appears as bright stripes or spots),
- Trachea and bronchial tree (appears as pipes with dark inside and bright borders),
- Fissures between the lung lobes (appears as hardly visible thin plate-like structures in light grey color).

Figure 1.4: An example of axial, sagittal and coronal views of a 3D chest CT scan.





Figure 1.5: A sketch of lung anatomy presenting main anatomical structures within human lungs: lobes, bronchial tree and vessels. *Reprint* from http://creationwiki.org/ *Respiratory_system*.

Figure 1.6: Lung anatomy in CT scan. Clearly visible vessels in red color, bronchial tree in blue color. Fissures between the three lobes in right lung are indicated by arrows. A magnified example of a sample within lung tissue is displayed in the bottom right corner.

Figure 1.5 shows a drawing of human lung anatomy. The right lung consist of three lobes and the left lung consist only of two lobes. Air enters the lungs first through the trachea and then spreads into the bronchial tree. Blood travels through the vessels and spreads in the lungs. Figure 1.6 shows how the corresponding anatomical lung structures appear in a CT scan, for visualization purposes only a coronal CT slice is shown.

1.3 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) encompasses both small airway disease and emphysema. The main topic of the thesis is emphysema, it is

characterized by irrevirsible destruction of lung parenchyma [5]. Due to the fact that both diseases usually coexist, the common term COPD is used for diagnostics. The most important risk factors of COPD are tobacco smoking and air pollution. COPD cause a shortness of breath, cronical cough, sputum production and may progressively lead to death.

COPD is presently estimated to be the fourth leading cause of death in the world [5]. Accordingly to the World Health Statistics report in 2008, COPD is predicted to be the third leading cause of death worldwide after ischaemic heart disease and cerebrovascular disease in 2030 [6].

Pulmonary function tests (PFT) or lung function tests (LFT) are the primary tools for diagnosis of COPD. Spirometry is the most common test in clinical practice, it measures vital lung characteristics, such as the maximum amount of air exhaled in the first second (FEV1, first expiratory volume in 1 second) and forced total amount of exhaled air (FVC, forced vital capacity). These methods are accepted worldwide for diagnosis of COPD, however there are several drawbacks to the lung function tests. The lung function tests are confirmed to lack sensitivity on the early stages of COPD; can not distinguish type of the abnormality (e.g. emphysema or airway disease) and spatial distribution of disease; and have poor reproducibility [7, 8, 9, 10].

Based on the LFTs, COPD is characterized into four stages; mild, moderate, severe and very severe COPD [5]. Based on the conventional diagnostic tools, disease progression could be determined only in the subjects, who change the COPD stage. A continuous measure of disease progression can be obtained from the lung function tests, but due to lack of sensitivity and reproducibility, the accurate monitoring of COPD is a difficult task in longitudinal studies. Computed Tomography offers a powerful alternative for examination of COPD. CT analysis allows both detailed visual assessment and the whole-lung quantification of emphysema extent via lung densitometry.

Emphysematous regions appear as areas with low-attenuation in CT scans of lungs, suggesting that CT image intensities can be used to quantify the severity of emphysema. Averaged lung density, *n*-th percentile density, and relative area with attenuation below, e.g. -910HU (emphysema index, RA-910HU) have all been successfully applied as emphysema measures. For detailed description of the computed tomography methods for lung disease quantification I refer reader to the book written by Webb R.W. et al. [11].

1.4 Monitoring Regional Disease Progression using Lung CT scans

In a longitudinal study, the lung densitometry from CT scans provides a continuous measurement of disease progression [12, 13, 14, 15, 16, 17, 18]. In a recent study on monitoring emphysema progression in Alpha-1 Antitrypsin deficiency subjects [16], the CT densitometry is reported to be significantly more sensitive than the conventional lung function test, the FEV1.

Although computed tomography offers a more promising alternative to spirometry, the CT scores of emphysema are global measures quantifying the disease in the complete lung. Lung partitioning is an approximate solution that allows quantification of emphysema and further monitoring of the disease progression in different regions of the lungs [12]. Another option of monitoring regional emphysema progression is enabled via segmentation methods. The state-of-the art segmentation methods provide anatomical partitioning of lungs into lobes [19, 20, 21], thereby allowing to monitor emphysema progression on a scale of a single lobe. Further segmentation of the lungs into pulmonary segments is extremely challenging task. There is no gold-standard method for segmentation of lung segments, since there are no clear boundaries between the segments, and even manual annotation of pulmonary segments is difficult. Several methods has been proposed for segmenting lung segments [22, 21], but it is still remains a difficult problem without a gold-standard. With use of segmentation methods alone, quantitative analysis of the emphysema will be always limited to the scale of reliably segmented structures. A CT lung scan provides detailed information of the lungs on a scale of 1 mm, thus potentially allowing to perform analysis of lung structures on a much smaller scale than the limiting scale of currently available segmentation methods.

For the detailed analysis of longitudinal changes in lungs, one needs an accurate spatial correspondence between the CT scans. Human observers possess a natural ability of determining corresponding structures in the two dimensional images. However, the task of determining corresponding structures in three dimensions is extremely difficult and time consuming for humans. Furthermore, the human vision system could easily recognize the same object but lacks the sensitivity to the spatial location, e.g., a small translation or distortion to the image may be left unnoticed. Therefore, for an accurate and efficient local analysis of longitudinal CT scans we need an automatic procedure, that will establish a point-to-point correspondence between the CT scans, the **image registration procedure**. Recent studies reported that an image registration procedure could provide comparable accuracy of the spatial correspondence with the human inter-observer variability [23, 24].

The following example in Figures 1.7-1.8 illustrates how an image registration facilitates monitoring of disease progression on an example of two CT lung scans of the same subject taken with a time interval of approximately two years. The axial, sagittal and coronal slices from the baseline CT scan are showed in the Figure 1.7a and the approximately the same slices from the follow up scan are displayed in Figure 1.7b. In both the baseline and the follow up images a bulla

Figure 1.7: An example of a subject with clearly visible pathology (bulla in the right lung indicated by red box) from the DLCST.



(a) Axial, sagittal and coronal slices from a baseline lung CT scan.



(b) Approximately the same axial, saggital and coronal slices from the follow up scan.

is presented in the right lung. Bulla, or air bubble, is a complication of the emphysema and may be treated by surgical removal or bullectomy.

Consider that subject location was identical in the baseline and the follow up scans, a simple subtraction of the two CT scans should reveal longitudinal changes of the bulla. However direct subtraction of the two images, Figure 1.8a, shows ambiguous and misleading information because of the two main reasons: subject location is not the same in the two CT images; breathing level at the two examinations vary significantly thus resulting in non homogeneous local deformations. After obtaining point-to-point correspondence between the images, the follow up image was deformed to the system of the coordinates of the baseline image and then subtracted from the baseline image. Figure 1.8b shows the final subtraction image and now, once the two images are properly aligned, the subtraction image reveal substantial increase of the bulla size.

Image registration of chest CT scans was successfully used for monitoring nodule growth [25, 26, 27]. Recently image registration has been used to estimate the progression of interstitial lung disease [28]. The benefits of image registration for

Figure 1.8: An example of how an image registration procedure is used for monitoring disease progression in a sequence of longitudinal CT scans.

(a) Direct subtraction of the follow up lung CT(b) Subtraction of the deformed follow up CT scan from the baseline CT scan after the image registration procedure is applied.

monitoring emphysema progression was investigated in this thesis in Chapters 6-7 [29, 30] as well as by other research groups [31].

1.5 Overview of Image Registration Methods

This section presents a brief overview of existing image registration methods, for the details I refer the reader to the concise but mathematical book by J. Modersitzki [32] or to the handbook on medical image analysis by M. Sonka and J.M. Fitzpatrick [33].

Image Registration Formalism

The starting point of any registration algorithm is a pair of images I_f (fixed image) and I_m (moving image). Other definitions of the I_f and I_m exist in the literature: image registration methods for lung CT scans define the fixed image



Figure 1.9: Discrete image as a continuous function of space coordinates.

(a) An axial slice of a lung CT scan with the zoom



(b) The intensity function plotted as surface of the spacial coordinates

as reference image [32, 34, 35, 36, 37, 38]; or target image [39, 40, 37, 41, 42]. The moving image also appears as template image [32, 40]; source image [39, 42]; floating image [38]; or test image [36]. In this thesis I will use the terms fixed and moving images, because these names reflect the essential functions of the images: while the fixed image remains fixed during the registration procedure the moving image is being deformed.

The task of image registration is to establish point-to-point correspondence between the two images. In case of lung CT scans, images are three dimensional and have discrete nature, the intensities are defined in a finite set of voxels $I_f(\mathbf{x}) = I_f(x_1^i, x_2^j, x_3^k)$. Figure 1.9a shows an example of an axial slice of a CT lung scan and a magnified area within lungs region. The zoomed image illustrates discrete nature of the lung CT scan. By means of the interpolation function, images may be defined in a continuous space of the spatial coordinates $I_f(\mathbf{x})$. Figure 1.9b displays a surface - the continuous linear approximation of the image intensities. This is the first fundamental part of the registration the **interpolation function**.

The registration procedure establishes point-to-point correspondence between the fixed image region $\Omega_f \subset \mathcal{R}^3$ and the moving image region $\Omega_m \subset \mathcal{R}^3$. The required point-to-point correspondence is defined in natural sense, e.g., an anatomical structure presented in the fixed image in a point $\mathbf{x} \in \Omega_f$ corresponds to the same anatomical structure presented in the moving image in a corresponding point $\mathbf{y} \in \Omega_m$. The formal definition of the correspondence is given via the associated transform function $T : \Omega_f \to \Omega_m$, which takes a point $\mathbf{x} \in \Omega_f$ and provides a corresponding point $\mathbf{y} \in \Omega_m$, $T(\mathbf{x}) = \mathbf{y}$. This is the second important part of the registration - the **transform function**. For the obtained transform function we can compute the resulting deformation vectors of every voxel in the fixed image grid $\vec{d}(\mathbf{x}) = \mathbf{y} - \mathbf{x}$. The two terms deformation field and transform function are equally common and usually interchangeable in the image registration literature.

Given a transform function T, one can evaluate the quality of the obtained point-to-point correspondence by first deforming the moving image $I_m \circ T$ =



Figure 1.10: Diagram displaying the image registration procedure and illustrating the interactions between the image registration components.

 $I_m(T(\mathbf{x}))$ and comparing the deformed image with the fixed image I_f using a (dis)simularity function $C(I_f(\mathbf{x}), I_m(T(\mathbf{x})))$. This is the third component of the registration - the (dis)similarity function. The (dis)similarity function could be applied directly to the images or to features extracted from the original images. For particular medical applications, an additional constraint on the transform function is needed, the **regularizer**. The (dis)similarity and the regularizer are both combined into a **cost function**, which balances between the (dis)similarity of the images and the regularity of the transform.

Finally, in the task of finding the best possible transform that defines pointto-point correspondence between the two images the minimum of the cost function should be obtained, therefore the following optimization problem should be solved:

$$\underset{T}{\operatorname{argmin}}(C(I_f, I_m \circ T)). \tag{1.1}$$

The final part of the registration procedure is the **optimization method** used to solve problem (1.1). The complete diagram displaying the workflow of image registration is given in Figure 1.10.

Evaluation of an Image Registration Method

It is always helpful to first check image registration results visually by comparing the fixed image with the deformed moving image. The deformed moving image could be assessed by displaying it side-by-side with the fixed image, or by displaying a checkerboard between the two images, or displaying the difference between the two images. The disadvantage of the first two methods is that with the side-by-side comparison the human eye could leave a small translation unnoticed and the checkerboard image limits the comparison to the size of the blocks, while in the difference image the mis-registrations are immediately visible.

Generally two classes of quantitative evaluation methods for assessing the quality of registration methods exist: explicit methods that assess the spatial accuracy of alignment in physical units usually millimeters; and implicit methods. The latter methods measure quality of the registration by first deforming the moving image and then comparing it with the fixed image using various (dis)similarity functions, e.g., cross-correlation coefficient, mutual information or sum of squared differences of the two images.

The explicit methods assess the spatial accuracy of the registration by means of, e.g., manually annotated corresponding points, landmarks, in the fixed and the moving images. The Euclidean distance between the landmarks of the moving image and deformed landmarks of the fixed image, the target registration error (TRE), is the quantitative measure of registration accuracy.

Manual annotation of landmarks is both time consuming and difficult for a pair of three dimensional images, therefore automatic or semi-atomatic alternatives were developed for detecting corresponding points in the image pairs. The semi-automatic methods ease the procedures of manually landmarking by suggesting possible corresponding points [39, 23]. Betke et al. [25] proposed a fully-automatic system for detecting corresponding landmarks such as trachea, sternum and spine in chest CT scans.

Another fully-automatic alternative to landmarking is assessment of spatial accuracy via presegmented anatomical lung structures. The distance between the correponding anatomical structures in the fixed and moving images, e.g., lung surfaces, lobe fissures, airway trees or vessel trees, estimates the spatial accuracy of the registration. The Euclidean distance could be computed by first deforming the anatomical structure segmented from the fixed image and then computing the distance to the same structure in the moving image. However, manually annotated landmarks remain the gold standard for the evaluation of image registration accuracy.

Examples of Image Registration Methods for Lung CT scans

The aim of this section is to give a brief overview of modern image registration methods used for lung CT images including the work presented in this thesis as well as work by other authors. Complete overview of general image registration methods could be found in [43].

Depend on the type of information that is being used in the registration algorithm, two classes of image registration methods could be defined: feature-based and intensity-based registration methods. The first class refers to the registration algorithms, where features are first extracted from the original intensity images and then the point correspondence is established using the obtained features. An examples of a feature-based method is landmark-based registration where the manually annotated landmarks used to align the images [44]. Another example is registration of segmented anatomical lung structures such as vessel trees and lung surfaces [37, 45], Chapter 3[46].

The intensity-based methods directly use the original intensities of the images. These methods are generally more widely used for lung CT images [47, 48, 38, 49, 50, 23, 51, 52, 53, 54, 55, 45, 56], Chapter 2[29]. Also joint registration algorithms where intensity is combined with the features were developed for lung CT scans [57, 58, 59], Chapter 4[60].

Depend on the type of the underlying deformation model, registration methods can be further classified into parametric and non-parametric registration. In parametric methods the transform is parameterized by a number of control parameters. The example of the parametric transform is a B-Spline transform, where the deformation is parameterized by a deformation vectors defined in grid points. Image registration with B-Spline transform was pioneered by D. Rueckert [61] and was first applied to the lung CT scans by D. Mattes [36]. The following registration methods of lung CT scans use the B-Spline transform [47, 48, 38, 49, 50, 23, 29, 51]. In contrast to the parametric methods, in non-parametric methods the deformations are assumed to fulfill a certain physical model, e.g., deformations of fluid [52, 53], proposed by Christensen G. et al. [62] and further developed by M. Bro-Nielsen [63]; elastic material [55, 45], first proposed by Briot C. et al. [64] and further developed by Bajcsy R. et al. [65]; or the optical flow methods [56], first proposed by Horn B.K.P. and Schunk B.G. [66]. While in the first group of methods, the deformation field is free-form and in any point it is interpolated from the deformations defined at the grid positions, in the latter methods the deformation field is obtained from the solution of the associated system of partial differential equations. Overview and implementation details of the latter methods could be found in PhD Thesis by M. Bro-Nielsen [63].

1.6 Outline of the Thesis

This thesis contains 8 chapters, including the general introduction in Chapter 1 and general discussion and conclusion in the final Chapter 8. The results of the novel scientific investigations are described in the Chapters 2, 3-7. A brief outline for each of the chapters is given below.

Chapter 2 describes a novel intensity-based image registration method developed specifically for registering intra-subject lung CT scans. The registration method is based on the widely used free form image registration via B-Splines [61]. The novelty of the developed method is in the proposed model of lung tissue ap-

pearance in CT scans during inspiratory cycle. The lung appearance in CT depends significantly on the amount of air inhaled. First because the lungs are larger in size at the inspiration level and second because the lung tissue saturates additional air and appear darker in CT scans which should not be confused with the emphysema progression and lung tissue destruction. We investigated the validity of the assumption that mass of lungs is preserved during the breathing cycle. The mass preserving assumption was incorporated into the image registration procedure and verified on a large set of lung CT scans with varying quality, ranging from small to large differences in inspiratory level.

Chapter 3 presents a new feature-based image registration where lung anatomical structures are used to establish a point-to-point correspondence. Three types of registration methods are evaluated: a curve-based registration method where the lung vessel centerlines are used to establish correspondence between the scans, the surface-based registration method where the lung surfaces are used for registration, and the combined method where both curves and surfaces are incorporated into a feature-based registration. The potential advantage of a featurebased registration method over intensity-based method is for diseased subjects, where intensity may change significantly because of the development of the disease. The proposed feature-based registration method does not require any point correspondence, thus it may be applied even using an incomplete and inconsistent segmentations.

Chapter 4 presents a combination of the intensity- and feature-based registration methods of Chapters 2 and 3. The deformations in the intensity-based method are constrained locally with the deformations obtained from the featurebased method. The weak point of intensity-based registration method is its dependence on the image gradient, thus favoring the good registration of the structures with high gradients, while disregarding misalignment of small unclear structures like the peripheral vessels. On the other hand the feature-based registration assigns the centerlines of small vessels and of large vessels the same value, therefore leading to equally accurate alignment of small and large vessels. The potential benefit of the combined approach is that final alignment is more accurate and realistic.

Chapter 5 presents results of the challenge "Evaluation of Methods for Pulmonary Image Registration 2010" (EMPIRE10) conducted in conjunction with the Grand Challenges in Medical Image Analysis Workshop in 2010. The mass preserving registration method from Chapter 2 was registered for the competition and final results are included into the thesis.

Chapter 6 presents an application of the intensity-based image registration method, described in the Chapter 2, for monitoring regional disease progression in longitudinal image studies. Areas with lower intensity in the follow up scan compared with intensities in the deformed baseline image indicate local loss of lung tissue that is associated with progression of emphysema. To account for differences in lung intensity owing to differences in the inspiration level in the two scans rather than disease progression, we propose to adjust the density of lung tissue with respect to local expansion or compression such that the total weight of the lungs is preserved during deformation. Our method provides a good intensity-based estimation of regional destruction of lung tissue for subjects with a significant difference in inspiration level between CT scans and may result in a more sensitive measure of disease progression than standard quantitative CT measures.

Chapter 7 presents new methodology and experimental results on monitoring local emphysema progression. We extended the framework from the Chapter 6. Follow up images were first registered to the baseline image and then local image dissimilarities were computed in the corresponding anatomical locations indicating the amount of local changes between the images. Experiments were conducted on patients from the longitudinal study of Alpha-1 Antitrypsin deficiency subjects scanned five times during a period of three years.

The final **Chapter 8** presents general discussion and gives a brief overview of future perspectives.

In this thesis, I used four different lung CT datasets: the pairs of CT scans taken at full inspiration breathhold from the Danish Lung Cancer Screening Study [67] in Chapters 2 and 6; pairs of lung CT scans taken at maximum and minimum breathhold from the study of children with cystic fibrosis (CF) at Sophia Children's Hospital [68] in Chapter 2; the pairs of end inspiratory and end expiratory phases of 4D-CT lung scans from the publicly available dataset [39] in Chapters 3 and 4; the pairs of CT scans taken at full inspiration breathhold from the EXAcerbations and Computed Tomography scan as Lung End-points (EXACTLE) Trial Study [16] in Chapter 7.

The following open source software packages were used to develop the described methods: ITK [69], CImg [70], elastix [71, 72], iso2mesh [73], exoShape^{*}.

^{*}To be released at http://www-sop.inria.fr/asclepios/software.php

Chapter 2

Mass Preserving Image Registration for Lung CT

In theory there is no difference between practice and theory, in practice there is.

— JAN L. A. VAN DE SNEPSCHEUT.

This chapter is partially based on the publications "Weight Preserving Image Registration For Monitoring Emphysema Progression", Gorbunova V., Lo P., Ashraf H., Dirksen A., Nielsen M., de Bruijne M., in proceedings of Medical Image Computing and Computer Assisted Intervention Conference in 2008 and "Mass Preserving Registration for Lung CT", Gorbunova V., Lo P., M. Loeve, H. Tiddens, Nielsen M., J.Sporring, de Bruijne M., in proceedings of Medical Imaging SPIE Conference in 2009.

2.1 Introduction

Registration of lung CT images is increasingly used in various clinical applications. Three main applications may be distinguished as follows [74] : atlas registration based segmentation of the lungs and structures within the lungs; registration of longitudinal CT image series to monitor disease progression; registration of successive frames in dynamic CT sequences to estimate local ventilation and perfusion. Examples of the first application can be found in [75, 20]. Sluimer et al. [75] proposed to segment lungs containing dense pathologies by non rigidly registering a set of segmented example images to the image to segment and propagating their labels, while Zhang et al. [20] used atlas registration to initialize fissure detection for lung lobe segmentation. Registration of scans of the same patient taken at different points in time is applied for instance in the monitoring of lung nodules, both to robustly match nodules in sequential CT scans [26, 27] and to visualize nodule changes over time [50]. Recently, registration was also applied to estimate local emphysema progression from longitudinal image data [29, 31]. Registration of successive time frames of 4D-CT lung images is used for motion estimation in lung cancer radiotherapy planning [49, 55, 76] and for estimation of regional lung ventilation [52, 45, 77, 42, 35]. The end expiratory lung CT scans was registered to the end inspiratory scans to facilitate classification of pulmonary diseases [78].

A crucial factor in image registration is the choice of a similarity measure describing the (dis)similarity between the fixed and the deformed images. Commonly used image similarity functions are the sum of squared differences (SSD), mutual information (MI) and normalized cross correlation (NCC) [79].

For intra-subject registration of lung CT images, which is the case we consider in this chapter, SSD is probably the most commonly used similarity measure [48, 27, 52, 53, 80, 81]. Sum of squared differences is optimal when corresponding anatomical points are represented by the same intensity in the images, with additional Gaussian noise. This is a valid assumption because Hounsfield unit (HU) in CT scan represents the density of tissue. Densities of the same tissue is often expected to remain constant in different scans. Previous studies on lung CT scans showed that density of lung tissue depends on regional ventilation and changes during breathing [82, 81]. The basic assumption of SSD similarity function does not hold for lung tissue and as a possible solution we propose to model appearance of lung tissue in CT scan with respect to the regional ventilation using a simple law of mass preservation.

In the mass preserving model, density of the lung tissue is inverse proportional to the local volume. Therefore change in local volume could be computed from the change in the density. First, Simon et al. [83] proposed this model and applied it to estimate regional ventilation from image intensity in 4D-CT lung scans. Vice versa, the change in density of the lung tissue could be computed from the change in the local volume. Under applied local deformations the density of the lung tissue is directly proportional to the determinant of the Jacobian of the transform function, associated with the deformations. Recently, Reinhardt et al. [52] showed strong correlation between regional ventilation obtained from the Xe-CT image and the ventilation computed from the image registration procedure. In the latter case, regional ventilation was computed from the determinant of Jacobian of the obtained transformation between the two images. Several recent studies have incorporated mass preserving assumption in registration process. Sarrut et al. [81] proposed to modify lung density in a 4D-CT image prior to registration. Tannenbaum et al. [84] proposed a completely new registration method which establishes the optimal mass transportation between the images while the image intensities remain constant. Castillo et al. [56] proposed to incorporate the mass preserving intensity modification model into the optical-flow registration and applied it to the 4D-CT images.

We developed our registration method based on the results from [52] and modeled the lung tissue density using the determinant of the Jacobian of the transform function. We modified the sum of squared differences similarity function to enable mass preservation and continuously simulated the appearance of the lung tissue under the given deformations.

Early versions of this work appeared in [29]. Since then a similar idea has been used by Yin et al. [85, 38], where the mass preserving image registration was applied to breath-hold lung CT images acquired at the maximum inspiration and maximum expiration in the same scanning session. We previously applied mass preserving algorithm to the pairs of maximum inspiration and maximum expiration CT scans taken on the same day [86].

In this chapter, we present the registration framework in more detail, investigate the assumption of mass preservation, and present a quantitative evaluation of registration accuracy of the proposed mass preserving image registration method compared to a standard image registration method on a large number of CT scans of varying quality, ranging from small to large differences in inspiration level.

2.2 Mass preserving image registration

This section briefly presents a general deformable image registration framework based on B-Splines which is used in many medical imaging tasks [61, 36], and explains how the proposed mass preserving methodology can be incorporated in this framework.

2.2.1 Image Registration Outline

Consider a pair of images I_f and I_m , referred to as fixed image and moving image respectively. The task of registration is to find for every point in the fixed image domain Ω_f the corresponding point in the moving image domain Ω_m . The obtained point correspondences defines a general transform function $T: \Omega_f \to \Omega_m$. Validity of the transform can be assessed by comparing the deformed moving image and the fixed image using a dissimilarity function $C(I_f, I_m \circ T)$. An optimal transform should minimize the dissimilarity between the deformed and fixed image, therefore the registration process can be formulated as a minimization problem, as follows,

$$\underset{T}{\operatorname{argmin}}(C(I_f, I_m \circ T))$$

2.2.2 Preprocessing

To improve registration performance, segmentations of the lung fields are obtained using region growing and morphological smoothing [87]. Previously, several papers showed better performance of registration if the rib cage was erased from the images [23, 48]. To remove the influence of the rib cage, we extract the lung area from the images and set the background to 0HU. Finally, the image intensities are shifted with a value 1000HU so that the new intensities approximate the real densities of the tissues.

2.2.3 Transformation

We follow a common approach and use a multi-resolution image registration strategy. First, the images are registered affinely. To provide an accurate initialization of the affine transform, the trachea and main bronchi are first extracted using a modified fast marching algorithm [87]. The center of the affine transform is then set at the carina point in the fixed image and the initial translation is set to the difference between the carina points in moving and fixed images. Secondly, a series of B-Spline transforms, with corresponding Gaussian smoothing at the coarser levels, is applied to the pre-aligned images. The final transform is thus a composition of a global affine transform T_A and N levels of B-Spline transforms $T_{\text{B-Spline}}^i$ with decreasing grid size:

$$T_{\text{final}}(\mathbf{x}) = T_{\text{B-Spline}}^{N} \circ \dots \circ T_{\text{B-Spline}}^{1} \circ T_{A}(\mathbf{x}), \qquad (2.1)$$

where $\mathbf{x} = (x_1, x_2, x_3)$ is a point in the fixed image domain Ω_f .

In this work, we have used small step size along the gradient and multi-level B-Spline grid to ensure that the transform is invertible [88].

2.2.4 Mass Preserving Similarity Function

We use the sum of squared differences similarity function as the basis for the mass preserving similarity measure,

$$C(I_f, I_m \circ T) = \frac{1}{|\Omega_f|} ||I_f(\mathbf{x}) - I_m(T(\mathbf{x}))||_{L_2}^2,$$
(2.2)

where \mathbf{x} is a point in the region Ω_f occupied by the fixed image I_f , $\mathbf{y} = T(\mathbf{x})$ is the corresponding point in the region Ω_m occupied by the moving image I_m .

The sum of squared differences is an optimal similarity measure if image intensities are identical or differ with Gaussian noise. This assumption does not hold in case of lung CT images, where both blood and air enter the lungs during inhalation. We used a hypothesis that majority of incoming blood stays in the larger vessels, and only air is inhaled into the alveoli. Therefore we can presume that mass of parenchyma remains constant and the density of lung tissue is inverse proportional to the amount of air. Under the applied local deformations, the induced change in local volume is defined by the determinant of Jacobain of the associated transform function.

Using the mass preserving assumption, the intensity of the moving image I_m in a point $\mathbf{y} \in \Omega_M$ is inverse proportional to the change in local volume $\frac{1}{det(J_{T^{-1}})}$ in the point \mathbf{y} . The modeled intensity can be written $\hat{I}_m(\mathbf{y}) = [det(J_{T^{-1}}(\mathbf{y}))]^{-1} I_m(\mathbf{y})$. Assuming that the transform function T is invertible, the determinant of Jacobian $J_{T^{-1}}(\mathbf{y})$ is the inverse of the determinant of Jacobian $J_T(\mathbf{x})$ and the modeled intensity of the moving image can be written $\hat{I}_m(\mathbf{y}) = det(J_T(\mathbf{x})) \cdot I_m(T(\mathbf{x}))$.

Finally, the mass preserving intensity model can be naturally incorporated in the standard sum of square differences similarity function:

$$C(I_f, I_m \circ T) = \frac{1}{|\Omega_f|} \int_{\Omega_f} [I_f(\mathbf{x}) - \det(J_T(\mathbf{x})) \cdot I_m(T(\mathbf{x}))]^2 d\mathbf{x}.$$
 (2.3)

2.2.5 Optimization

In this chapter we use a stochastic gradient descent method [51] to optimize the similarity function. The closed form expression for the gradient of the proposed mass preserving similarity function of (2.3) is,

$$\mathcal{D}_{\mathbf{a}}C = -\frac{2}{|\Omega_f|} \int_{\Omega_f} \left[I_f(\mathbf{x}) - \det(J_T(\mathbf{x})) \cdot I_m(T(\mathbf{x})) \right] \cdot \det(J_T(\mathbf{x})) \cdot (2.4)$$

$$\cdot \left[\operatorname{vec}(J^{-T}(\mathbf{x}))^T \cdot \mathcal{D}_{\mathbf{a}} \operatorname{vec}(J(\mathbf{x})) \cdot I_m(T(\mathbf{x})) - \mathcal{D}_{\mathbf{y}} I_m(T(\mathbf{x})) \cdot \mathcal{D}_{\mathbf{a}} T(\mathbf{x}) \right] \, d\mathbf{x},$$

where $\mathcal{D}_{\mathbf{a}}$ represents a gradient row vector operator with respect to the transform parameters \mathbf{a} , $\mathcal{D}_{\mathbf{y}}$ represents a spatial gradient vector operator, and $vec(\cdot)$ is the vector constructed by concatenating all columns of a matrix. The derivation of (2.4) is given in the Section 2.7.

In case of SSD similarity function, only voxels with non-zero image gradient contribute to the gradient thus resulting in a higher uncertainty of registration in homogeneous regions [47]. On the contrary, for the proposed mass preserving similarity function of (2.4), voxels where the image gradient $\mathcal{D}_{\mathbf{y}}I_m(\mathbf{y})$ is close to zero also contribute to gradient thus providing additional information in homogeneous regions.

2.3 Evaluation Strategy for Image Registration Accuracy

This section describes how the performance of image registration with the regular sum of squared differences similarity function (2.2) is compared to image registration with the proposed mass preserving similarity function (2.3). Evaluation of the registration procedure is done based on the vessel tree centerlines. Additionally, the registration accuracy on a subset of images is assessed using manually annotated landmarks.

The vessels are segmented using the algorithm described in [87]. First, the image is thresholded with fixed intensity $t_v = -380$ HU, followed by multi-scale local analysis of the Hessian matrix to remove non-tube like structures. Large vessels in the hylum area are discarded. Finally, centerlines are extracted from the segmented vessel tree using a 3D thinning algorithm [89]. Figure 2.1 shows an example of a segmented vessel tree and the centerlines extracted from it.



Figure 2.1: Surface rendering of segmented lung fields and vessels (a) and corresponding vessel centerlines (b).

We measure image registration accuracy using the Euclidean distance between vessel tree centerlines. First, we extract vessels from both moving and fixed images. Next, the moving image vessel tree is deformed according to the final transform coefficients. The vessel centerlines are extracted from the segmented vessel trees in fixed and deformed images. Then the Euclidean distance map is computed for the centerlines of the fixed image. Finally, the image registration error is computed as the Euclidean distance map value averaged over all centerline voxels in the deformed moving vessel tree.

2.4 Experiments and Results

Section 2.4.1 describes the parameter settings for the two registration methods used in all the conducted experiments. We performed three different experiments to study the proposed mass preserving assumption. First experiment, described in Section 2.4.2, was designed to evaluate the assumption of mass preservation and to investigate the relationship between the volume of lungs and appearance of lung tissue. Section 2.4.3 illustrates the behaviour of the two registration methods, the proposed registration with mass preserving similarity function (MP) and the registration with sum of squared differences similarity function (SSD), on a synthetic example. Finally, the third experiment in Section 2.4.4 was designed to investigate how the difference in lung volume effects the two registration methods.

2.4.1 Parameter Settings

We applied three levels of B-Spline transforms, N = 3, with decreasing grid size. The first two levels were applied to the deformed moving image blurred Gaussian $\sigma_{1,2} = 1$ voxel and sampled by a factor of two in each direction. The third level was applied to the full resolution image without smoothing. The number of grid cells in each B-Spline level was $3 \times 3 \times 3$, $6 \times 6 \times 6$ and $12 \times 12 \times 12$ respectively. Optimal parameters were obtained by minimizing the cost function between the fixed and corresponding moving images.

After each level of transform we computed the current deformation field as the sum of the deformation fields from the previous transforms. The original moving image was then deformed with the obtained deformation field and image intensities were adjusted with respect to the mass preserving model. The Jacobian of the transform was computed using a first order difference scheme with the step equal to the image spacing.

Each of the four transforms in (2.1) was optimized separately using the stochastic gradient descent [51]. The number of voxel samples was chosen proportional to the number of parameters to optimize but not smaller than 10^4 , and was set to $5 \cdot 10^4$ for the finest B-Spline transform and to 10^4 for the intermediate B-Spline and Affine transforms. Maximum number of iterations was 1000 for all the transforms. The maximum step length along the normalized gradient direction was set to 0.5 mm.

Vessel trees were segmented using the algorithm as in [87]. The intensity threshold was set to -400HU for the scans in the groups A-C, and -600 for the scans in the group D, and the ratio of Hessian eigenvalues was set to $m_1 = 0.5, m_2 = 0.5$ for the groups A-C and $m_1 = 0.75, m_2 = 0.5$, for the group D. For more details on the parameters of the segmentation algorithm we refer reader to [87].

2.4.2 Experiment 1: Relationship Between Mass, Volume and Density of Lungs

We selected 797 subjects which were scanned annually during 3 year period. All subjects did not suffer from Chronic Obstructive Pulmonary Disease (COPD) at the baseline and at the follow up visits according to the GOLD guidelines [5]. We generated all possible pairs of scans of the same subject and randomly selected 1430 image pairs. We computed total lung mass, total lung volume and average lung density for each pair of CT scans. Figure 2.2a shows the scatter plot between relative change in total lung volume and change in total lung mass for the image pairs. Figure 2.2b shows the scatter plot between relative change in total lung volume and change in total lung with mass and difference in average density. Spearman correlation between difference in mass and difference in volume was r = 0.14 (p < 0.001), and correlation between difference in average density and difference in volume was r = -0.91 (p < 0.001).

We investigated the relationship between total lung volume and the shape of histogram of a CT lung scan. We applied a simplified mass preserving model, where the lungs were assumed to expand or contract uniformly and the intensities were globally adjusted as

$$\hat{I}_1(\mathbf{x}) = \frac{V_1}{V_2} (1000 + I_1(\mathbf{x})) - 1000, \qquad (2.5)$$

where the I_1 is the first image in a pair, the V_1 and V_2 is the total lung volume of the first and the second images in the pair. The proposed adjusting model may result in missing intensity values, e.g., if the ratio of volumes is equal to $V_1/V_2 = 2$ the adjusted intensities will be only even numbers. In order to eliminate this artifact, the histograms were smoothed with Gaussian $\sigma = 5$ HU. Finally, the histograms were normalized to represent probability distribution of the intensities. The difference between the probability distributions of intensity values of lung parenchyma before and after adjustment was assessed using the Kullback-Leibler divergence.

The 1430 pairs of CT scans were split into 15 groups with the relative volume difference varying from -37.5% to 37.5% of the mean lung volume of the two scans. For each group, the average and the standard deviation of the Kullback-Leibler divergence is reported in the Figure 2.2c.

2.4.3 Experiment 2: Synthetic Data

The two image registration methods were evaluated on a synthetic image pair constructed to mimic lung tissue expansion under the mass preservation law. Both moving and fixed images represented uniform spheres placed in the center of the images with the background density 0 [g/L] (or intensity -1000HU). The moving sphere S_1 had radius $r_1 = 16$ mm and density $\rho_1 = 200$ [g/L] (or intensity value $I_1 = -800$ HU) and the fixed sphere S_2 had radius $r_2 = 20$ mm and density



Figure 2.2: Scatter plot (a) displays the correlation between relative change in total lung volume and change in total lung mass. Scatter plot (b) displays the correlation between relative change in total lung volume and change in average lung density. Average Kullback-Leibler divergence between histograms of two CT scans of the same subject before and after the global intensity adjustment is presented in plot (c).

 $\rho_2 = 100 \text{ [g/L]}$ (or intensity value $I_2 = -900 \text{HU}$). The mass of the two spheres was approximately equal, 1.93 g and 1.89 g respectively.

The initial affine transform was excluded from the image registration framework described in Section 2.2.3 and only the multi-level B-Spline transforms were used. Optimization parameters were identical for both image registration methods.

Figure 2.3 shows the original fixed (a) and the moving (b) spheres and the resulting difference between the registered and fixed images for the standard



registration method (c) and the mass preserving method (d).

Figure 2.3: The two image registration methods were applied to a synthetic example. The moving image (a) and fixed image (b) consist of spheres with equal mass, but different density. Results (difference image) of the standard image registration method (c) and the proposed mass preserving image registration method (d).

2.4.4 Experiment 3: Registration of Lung CT scans

The third experiment was conducted on a large number of lung CT scans of variyng quality, ranging from small to large differences in inspiration level.

- Group A: 44 image pairs of the same subject with the relative difference between total lung volumes for baseline and follow up images $\Delta TV < 2.5\%$;
- Group B: 44 image pairs of the same subject with the relative difference between total lung volumes for baseline and follow up images $\Delta TV > 9\%$;
- Group C: 16 image pairs of inspiratory and expiratory CT scans;
- Group D: 5 image pairs extracted at the end exhale and end inhale phases of the 4D-CT scans from publicly available database [39].

For all four groups, we measured performance of the registration algorithms using the proposed evaluation technique Section 2.3. For the last group, 300 manually selected landmarks for each image pair were available. In this group we additionally compared the two registration methods with the target registration error.

Longitudinal Study: Groups A and B

Two groups of low dose CT image pairs were selected from the Danish Lung Cancer Trial Study (DLCST) database [67]. Before the acquisition, subjects were instructed to hold their breath at maximum inspiration. Image pairs have a time interval between baseline and follow up of approximately one year. The in-plane resolution was 0.78×0.78 mm and the slice thickness was 1 mm. In group A the average relative difference between the baseline and follow up lung volumes was $1.23 \pm 0.77\%$ and in group B the average difference was $14.96 \pm 5.84\%$.

Evaluation results for the two image registration methods are presented in the Table 2.1. For each patient, we computed the average distance between centerlines registered with the standard method and with the proposed mass preserving method. The overall improvement for each data set is presented in Figure 2.4 with box plots showing median, lower and upper quartile, and skewness of the distribution within each group. The correlation between the relative difference in total lung volume and decrease in error of the mass preserving method in the two selected groups was r = 0.44 (p < 0.001).

Expiratory and Inspiratory CT Images: Group C

The group C in our experiment consists of sixteen children with cystic fibrosis (CF) monitored at Sophia Children's Hospital [68]. All children underwent biannual CT scanning during annual checkup during a clinically stable period. Each CT study consisted of a low-dose CT scan taken at maximum inspiration and an ultra low-dose scan taken at maximum expiration. Before the acquisition, subjects were instructed to exhale or inhale completely and to hold their breath. The in-plane resolution was on average 0.54×0.54 mm, the slice thickness is 2.5 mm with a slice overlap of 1.3 mm. The difference in inspiratation level between the two images was large and many of the expiration scans show regions of trapped air, indicating local inhomogeneity of deformation. On average, the difference between inspiratory and expiratory volumes was $48.27 \pm 19.69\%$. The inspiratory image was set as the fixed image.

Evaluation results are presented in the Table 2.1 and the overall improvement in the group C is presented in the box-plot Figure 2.4. Correlation between the relative difference in total lung volume and improvement of the mass preserving method in the selected group was r = 0.77 (p < 0.001). Figure 2.5 shows an example result of the two image registration techniques. The expiratory image was deformed according to the final transformation and subtracted from the inspiratory image. The two images show corresponding slices in the difference images for the mass preserving image registration technique 2.5a-2.5d and for the standard registration 2.5e-2.5h.

End Exhale and End Inhale CT Images: Group D

The last group D consists of 5 pairs of images from a publicly available dataset [39], where each pair consists of images extracted at the end exhale and the end inhale phases of 4D CT images. In-plane resolution of the images varied from 0.97×0.97 mm to 1.16×1.16 mm and slice thickness was 2.5 mm. The study [39] also provides 300 manually placed landmarks at the end exhale and end inhale phases of the 4D CT images. End exhale image was set as the fixed image.



Figure 2.4: Box plots showing the improvement in registration accuracy obtained by the mass preserving image registration method for each of the groups A-C. Each plot shows the median (central mark), lower and upper quartile (edges of the box), skewness of the distribution (notches) and outliers (crosses). From left to right: group A (44 subjects with average $\Delta TV = 1.23\%$), group B (44 subjects with average $\Delta TV = 14.96\%$), group C (16 subjects with $\Delta TV = 48.27\%$).

Table 2.1: Average registration accuracy in each group, assessed using the vessel centerline distance, for the registration with the mass preserving (MP) and the sum of squared differences similarity function (SSD). Number in brackets indicates the number of subjects in the group.

	Vessel Centerline Distance [mm]			
Group ΔTV [%] ΔTV [L]	SSD	MP	T-test	
A (44) $1.23 \pm 0.77 0.07 \pm 0.04$	1.541 ± 0.258	1.539 ± 0.251	p = 0.604	
B (44) 14.96 \pm 5.84 0.83 \pm 0.29	2.017 ± 0.634	1.987 ± 0.619	p = 0.028	
C (16) 48.27 \pm 19.69 1.53 \pm 0.94	3.959 ± 1.370	3.535 ± 1.046	p = 0.003	
D (5) 11.15 \pm 2.86 0.37 \pm 0.10	2.070 ± 0.519	2.038 ± 0.522	p = 0.160	

We validated accuracy of the two image registration algorithms using two independent validation methods. First, we validated using target registration error (TRE) between the landmarks. The mean and the standard deviation of TRE for each case is reported in the Table 2.3. The significance of the difference between the two registration methods is assessed using the Student t-test. Second, we evaluated the performance of the registration using the proposed evaluation method from Section 2.3. The mean and the standard deviation of the vessel centerline distance for each case is reported in the Table 2.3.



Figure 2.5: An example illustrating the registration performance of mass preserving image registration (a)-(d) and standard registration (e)-(h) for the same randomly selected subject from the group C. The difference images were constructed by first deforming the expiratory image and then subtracting it from the inspiratory image. Every 20th slice, selected in the range of 40 - 100 from the corresponding volumetric difference image is displayed from left to right.

Table 2.2: The two registration methods compared based on the proposed evaluation measure and the target registration error. Results of the validation based on the landmarks are reported before the registration (Initial), after the registration was applied with the mass preserving similarity function (MP), and with the sum of squared differences similarity function (SSD). The statistical comparison of the target registration errors is performed using Student's test and the p-value is reported in the last column.

	Target Registration Error, [mm]				
Ν	$\Delta TV\%$	Initial	MP	SSD	p-value
1	9.2	3.99 ± 2.75	1.15 ± 0.55	1.18 ± 0.56	p = 0.05
2	8.9	4.34 ± 3.90	1.26 ± 0.70	1.27 ± 0.68	p = 0.53
3	11.5	6.93 ± 4.09	1.79 ± 1.08	1.88 ± 1.12	p < 0.001
4	15.9	9.83 ± 4.86	2.01 ± 1.41	2.16 ± 1.54	p < 0.001
5	10.2	7.51 ± 5.53	2.31 ± 1.89	2.29 ± 1.82	p = 0.32
All	11.14	6.52 ± 4.83	1.70 ± 1.30	1.76 ± 1.32	p < 0.001

2.5 Discussion

2.5.1 Mass Preservation in Lung CT Scans

The experiment in Section 2.4.2 showed that the correlation between the change in average lung density and the change in total lung volume was much stronger

Table 2.3: The two registration methods compared based on the proposed evaluation measure and the target registration error. results of the evaluation based on vessel-centerline distance before the registration (Initial), after the registration was applied with the mass preserving similarity function (MP), and with the sum of squared differences similarity function (SSD).

	Vessel Centerline Distance, [mm]					
Ν	Initial	tial MP SSI				
1	3.16 ± 2.17	1.38 ± 1.61	1.43 ± 1.61			
2	4.64 ± 3.67	1.82 ± 2.35	1.80 ± 2.34			
3	5.15 ± 3.80	2.16 ± 2.78	2.25 ± 2.79			
4	4.86 ± 3.80	2.02 ± 2.26	2.05 ± 2.25			
5	6.35 ± 6.42	2.81 ± 3.68	2.82 ± 3.65			
All	4.83 ± 1.14	2.04 ± 0.52	2.07 ± 0.52			

(r = -0.91, p < 0.001) than the correlation between the change in lung mass and the change in total lung volume (r = 0.14, p < 0.001). This indicates a strong dependency of lung tissue appearance in CT image on the level of inspiration. The correlation between the change in mass of the lungs and the change in total lung volume was weak but significant. This may be due to the incomplete vessel extraction, since inspiration leads to increase in perfusion and therefore to increase in partial volume effect near the vessels.

A simplified intensity correction model based on the idea of mass preservation was investigated in the Section 2.4.2. Analysis of image histograms of healthy subjects from Figure 2.2c confirms the fact that the probability density function of image intensities significantly depends on the level of inspiration. Furthermore, the simplified global mass preserving intensity correction significantly reduced the divergence between the histograms as shown in Figure 2.2c.

2.5.2 Mass Preserving Registration of Lung CT Images

The experiment in Section 2.4.3, conducted on synthetic data, illustrated the principle advantage of the proposed mass preserving registration, where mass preserving image registration leads to the expected alignment of the two spheres equal in mass and different in volume. The SSD similarity function aligns equal intensities and in the presented synthetic data, intensities of the two spheres were different therefore the geometrically correct solution results in a larger value of the SSD similarity function than the initial positioning of the spheres. The mass preserving similarity function allows to align initially different intensities since the intensity can be changed during the registration procedure thus resulting in the expected alignment of the spheres.

Optimization for the sum of squared differences similarity function as well as

the proposed mass preserving similarity function is mainly driven by high gradient structures in the moving image. In areas where the image gradient is close to zero, the optimization of the mass preserving similarity function additionally incorporate the original image intensities. If the difference in intensities is induced by local difference in regional ventilation the optimization of mass preserving similarity function will follow the mass preserving model and align intensities correctly with respect to the measured local volume change.

The advantage of mass preserving image registration is further confirmed in the third experiment, especially in cases where the difference in lung volume is large, which implies differences in regional ventilation and density. The group A of subjects in our experiments had negligible difference in lung tissue appearance between the two CT scans, therefore the difference between the two methods was not significant (p=0.6). In the group B, mass preserving image registration resulted in a relatively small, but statistically significant, improvement in registration accuracy compared to the standard image registration method (0.03 mm, p=0.03). In group C, the most challenging group, a considerable and significant improvement was measured (0.43 mm, p=0.003). The improvement in registration accuracy in groups A-C was strongly correlated with the relative difference in lung volume (r = 0.78, p < 0.001). In the last group D, the improvement of mass preserving registration assessed via manually selected landmarks was 0.06 mm, and was statistically significant ($p \le 0.001$).

A mass preserving model predicts lung tissue appearance in CT scan during respiration based on a simple assumption: preservation of blood in lungs. The density of lung tissue is corrected locally, within the typical size of the B-Spline kernel, according to the change in regional ventilation as measured by the Jacobian of the deformation field. We previously applied this model for monitoring local emphysema progression in patients with COPD [29]. Recently, a similar study was done to monitor emphysema progression in patients with Alpha-1 antitrypsin deficiency patients [31], where a mass preserving intensity correction was applied after normal image registration to compensate for differences in inspiration level between scans. Results suggested more accurate estimates of the disease progression in both these studies.

2.5.3 Distance Between Vessel Centerlines as a Measure for Registration Accuracy

Manual extraction of landmarks is both time consuming and prone to interexpert variability. In this work, instead of relying on manual landmarking we used an automated evaluation method based on vessel tree centerlines to assess the registration accuracy, resulting in a large number of approximately corresponding landmarks throughout the lungs. The drawback of the proposed evaluation is that vessels that are segmented in only one of the scans may lead to inflation of errors, whereas the absence of point correspondence may lead to underestimation of errors especially in regions where vessel density is high. This could be improved for instance by determining corresponding vessel bifurcation points and parameterizing vessel segments in a consistent manner. However, the effects of over- and under-estimations should be similar for the two different registration methods of the same scan pair provided that both registration methods are reasonably good, and the vessel tree distance is therefore well suited to compare registration accuracy of different methods on the same images.

Comparison with landmark registration error (TRE) showed that the vessel distance measure underestimated the errors before the registration (the average vessel distance measure was 4.83 mm while the average TRE was 6.52 mm) and resulted in overall overestimation of errors after the registration (2.40 mm versus 1.70 mm respectively).

2.5.4 Comparison to Results in Literature

In the conducted experiments, the proposed mass preserving image registration was better than the registration with the sum of squared differences similarity function. The results of the registration with SSD similarity function was comparable with those reported in the literature. Most registration methods were evaluated on 4D-CT scans [39, 38, 48, 37, 80, 56].

Wu et al. [48] used manually extracted landmarks from four end exhale and end inhale image pairs from dynamic CT sequences to evaluate a B-Spline image registration algorithm and reported an average distance between landmarks of 2.78 mm. Pevsner et al. [80] analyzed 6 pairs of end-exhale and end-inhale CT lung scans registered using a fluid registration method with 41 landmarks and reported a discrepancy between registered and observer-determined landmarks of 2.9 mm on average. Vik et al. [37] evaluated a B-Spline image registration algorithm on a set of 10 pairs of end exhale and end inhale phases of 4D-CT lung scans with user-determined landmarks. The average distance between landmarks was 2.85 ± 3.06 mm. Castillo et al. [39] compared optical flow and landmarkbased image registration algorithms on 5 pairs of end inhale and end exhale 4D-CT images as in our experiments. The average accuracy was 6.9 ± 0.1 mm for the optical flow image registration and 2.5 ± 0.02 mm for landmark-based registration. Another study by Castillo et al. [56] reported the average TRE of 1.59 mm obtained on the first 3 pairs of the end exhale and end inhale phases of 4D-CT scans. The target registration error of the proposed mass preserving registration method applied on the same 5 pairs end inhale and end exhale phases of 4D-CT scans was 1.70 mm on average.

In our experiments on group C, the pairs of maximum expiration and maximum inspiration CT lung scans, the average vessel distance after the mass preserving registration was relatively large 3.53 mm. This group was the most challenging because of large difference in volume and large amount of pathology such as air-trapping and fibrotic tissue. In this group, the mass preserving registration showed clear improvement compare to the registration method with the SSD similarity function.

Registration of pairs of inspiratory lung CT scans generally produces more accurate results than can be obtained for expiration/inspiration scan pairs or end-exhale/end-inhale images from 4D-CT. Our experiments on longitudinal inspiratory CT lung scans showed comparable accuracy of mass preserving registration 1.76 mm to the results on similar studies reported in the literature [25, 23]. Betke et al. [25] evaluated an image registration algorithm on 10 pairs of repeated inspiratory CT scans using RMS between corresponding surface points and measured error of 3.7 mm. Murphy et al. [23] reported an average error of only 0.7 mm evaluated on a set of semi-automatically extracted landmarks. In the study, selection of landmarks was supported by a thin-plate spline landmark registration algorithm, potentially favoring smooth deformation fields.

2.6 Conclusion

In this chapter we investigated the assumption of mass preservation during breathing cycle on the large number of CT scans of varying quality, ranging from small to large difference in inspiration level. We incorporated the mass preserving model into a standard image registration method and evaluated it synthetic data and intra-subject lung CT scans. The results showed that the mass preserving model is a plausible model which describes the change in density in lung CT scans during breathing cycle. Furthermore, the performance of the image registration method with the mass preservation is superior for image pairs with a considerable difference inspiratory level than the image registration method without mass preservation assumption.

2.7 Appendix: Gradient of the mass preserving similarity function

In this section we derive the analytical expression for the gradient of the proposed mass preserving similarity function as given in (2.4). Consider the similarity function (as in (2.3)):

$$C(I_f, I_m \circ T) = \frac{1}{|\Omega_f|} \int_{\Omega_f} [I_f(\mathbf{x}) - det(J_T(\mathbf{x})) \cdot I_m(\mathbf{y})]^2 d\mathbf{x}, \qquad (2.6)$$

where $\int \circ d\mathbf{x}$ is a shortened notation of the volume integral $\int \int \int \circ dx_1 dx_2 dx_3$. The transform $\mathbf{y} = T(\mathbf{x})$ depends on the set of parameters \mathbf{a} , $T(\mathbf{a}, \mathbf{x})$. For simplicity, we shorten the notation of the Jacobian determinant $|J| = det(J_T(\mathbf{x}))$, the fixed

image value in a point \mathbf{x} as $I_f = I_f(\mathbf{x})$, the transformed point $\mathbf{y} = T(\mathbf{x}, \mathbf{a})$, the moving image value in the transform point $I_m = I_m(\mathbf{y})$ and label the observed difference in intensities at a point \mathbf{x} with respect to the transform parameters \mathbf{a} as a function $G(\mathbf{a}, \mathbf{x})$:

$$C(I_f, I_m \circ T(\mathbf{a})) = \int_{\Omega_f} G(\mathbf{a}, \mathbf{x})^2 \, d\mathbf{x},$$
$$G(\mathbf{a}, \mathbf{x}) = I_f(\mathbf{x}) - \det(J_T(\mathbf{x})) \cdot I_m(\mathbf{y}(\mathbf{a}, \mathbf{x})) = I_f - |J|I_m.$$

Using differential algebra we write the full differential of the similarity function,

$$dC(\mathbf{a}) = \int_{\Omega_f} 2G dG \, d\mathbf{x},$$

$$dG(\mathbf{a}, \mathbf{x}) = \mathcal{D}_{\mathbf{x}} I_f d\mathbf{x} - |J| \operatorname{tr}(J^{-1} dJ) I_m - |J| \mathcal{D}_{\mathbf{y}} I_m d\mathbf{y}$$

$$= \mathcal{D}_{\mathbf{x}} I_f \, d\mathbf{x} - |J| \left(\underbrace{\operatorname{tr}(J^{-1} dJ)}_{(*)} I_m + \mathcal{D}_{\mathbf{y}} I_m d\mathbf{y} \right), \qquad (2.7)$$

where the notation dC stands for the full differential of the function C. Using the definition of the vec operator, we can simplify the term (*):

$$\operatorname{tr}(J^{-1}dJ) = \operatorname{vec}(J^{-T})^T \operatorname{vec}(dJ).$$
 (2.8)

Further the term vec(dJ) can be expanded,

$$\operatorname{vec}(dJ) = d(\operatorname{vec}(J)) = \mathcal{D}_{\mathbf{a}}\operatorname{vec}(J) d\mathbf{a} + \mathcal{D}_{\mathbf{x}}\operatorname{vec}(J) d\mathbf{x},$$
 (2.9)

and by substituting (2.9) into (2.8) we get

$$\operatorname{tr}(J^{-1}dJ) = \operatorname{vec}(J^{-T})^T \cdot \mathcal{D}_{\mathbf{a}}\operatorname{vec}(J) \, d\mathbf{a} + \operatorname{vec}(J^{-T})^T \cdot \mathcal{D}_{\mathbf{x}}\operatorname{vec}(J) \, d\mathbf{x}, \qquad (2.10)$$

where $\mathcal{D}_{\mathbf{a}}$ is the gradient in the direction of the transform parameters \mathbf{a} and $\mathcal{D}_{\mathbf{x}}$ is a spatial gradient. The differential $d\mathbf{y}$ is defined as

$$d\mathbf{y} = \mathcal{D}_{\mathbf{a}}\mathbf{y}\,d\mathbf{a} + \mathcal{D}_{\mathbf{x}}\mathbf{y}\,d\mathbf{x} = \mathcal{D}_{\mathbf{a}}\mathbf{y}\,d\mathbf{a} + J\,d\mathbf{x}.$$
(2.11)

By substituting (2.10) and (2.11) into (2.7) we get the full differential of $C(I_f, I_m \circ T)$:

$$dG(\mathbf{a}, \mathbf{x}) = \mathcal{D}_{\mathbf{x}} I_f \, d\mathbf{x} - |J| \cdot \mathcal{D}_y I_m \cdot J \, d\mathbf{x} - |J| \cdot I_m \cdot \operatorname{vec}(J^{-T})^T \cdot \mathcal{D}_x \operatorname{vec}(J) \, d\mathbf{x} - |J| \cdot \operatorname{vec}(J^{-T})^T \cdot \mathcal{D}_{\mathbf{a}} \operatorname{vec}(J) \, d\mathbf{a} \cdot I_m - |J| \cdot \mathcal{D}_y I_m \cdot \mathcal{D}_{\mathbf{a}} \mathbf{y} \, d\mathbf{a}.$$

Finally, since \mathbf{x} is fixed, we find that the partial derivative of $C(I_f, I_m \circ T)$ w.r.t. the transform parameters \mathbf{a} is

$$\mathcal{D}_{\mathbf{a}}C = -\frac{1}{\Omega_f} \int_{\Omega_f} 2(I_f - |J| \cdot I_m) |J| \left(\operatorname{vec}(J^{-T})^T \cdot \mathcal{D}_{\mathbf{a}} \operatorname{vec}(J) \cdot I_m - \mathcal{D}_{\mathbf{y}} I_m \cdot \mathcal{D}_{\mathbf{a}} \mathbf{y} \right) \, d\mathbf{x},$$

where $\mathcal{D}_{\mathbf{y}}I_m = (\partial_{y_1}I_m; \partial_{y_2}I_m; \partial_{y_3}I_m)$ is the spatial row-vector gradient and $\mathcal{D}_{\mathbf{a}}$ is the row-vector gradients the transform $T(\mathbf{x}) = \mathbf{y} = (y_1; y_2; y_3)$ in the direction of the transform parameters \mathbf{a} ,

$$\mathcal{D}_{\mathbf{a}\mathbf{y}} = \begin{pmatrix} \partial_{a_1}y_1 & \dots & \partial_{a_n}y_1 \\ \partial_{a_1}y_2 & \dots & \partial_{a_n}y_2 \\ \partial_{a_1}y_3 & \dots & \partial_{a_n}y_3 \end{pmatrix}.$$
 (2.12)

Chapter 3

Curve- and Surface-based Registration of Lung CT images via Currents

This chapter is based on the publication "Curve- and Surface-based Registration of Lung CT images via Currents", Gorbunova V., Durrleman S., Pechin L., Pennec X., de Bruijne M., in proceedings of The Second International Workshop on Pulmonary Image Analysis in conjunction with the Medical Image Computing and Computer Assisted Intervention Conference 2009.

3.1 Introduction

Registration of chest CT scans is an important topic within pulmonary image analysis. The general task of registration is to establish a point-to-point correspondence between two images. Registration of lung CT images can be used in various clinical applications, such as lung cancer radiotherapy planning and quantitative analysis of disease progression.

Image registration methods can be separated into two general groups: intensitybased and feature-based methods. Intensity-based methods integrate spatial information over the entire image domain, whereas feature-based methods require a representation of the image data in terms of distinctive geometrical structures. Feature-based methods offer more robust registration when image intensity is changed, for instance owning to pathology, image artifacts or differences in scan protocol. Generally, segmentation of geometrical structures in lungs is less sensitive to intensity changes, since a segmentation method incorporates geometrical regularity constraints or prior anatomical knowledge. Moreover, segmentation of distinctive lung structures may be either corrected manually or delineated by a professional.

The most distinctive anatomical structures in lung CT images are vessels, airways, lobe fissures and lung surfaces. Deformation of lungs surfaces and lobe fissures provide an insight into the global motion of the lungs, while deformations of vessels and airway tree characterize small-scale deformations inside the lungs.

A feature-based registration relies on various geometrical structures, e.g., points, curves or surfaces. Thin-plate spline image registration [44, 90, 91] is the standard method for matching points under the assumption that deformations are small. For large deformations, a diffeomorphic point matching approach was developed by Joshi and Miller [92] and was later adapted for surface matching [93]. Current-based diffeomorphic method for surface matching under the large deformations, pioneered by Glaunès et. al. [93], was further developed and adapted for curve matching problem [94, 95]. Within a framework of currents, no point correspondence between structures is required.

Several surface-based registration methods were previously developed for lung CT images [37, 76, 25]. The outer surface of the lungs together with the outer surface of vessels were used in an algorithm similar to iterative closest point methods in [37]. Lung surfaces were used to register CT lung images [25] and to constrain intensity-based registration with a deformation field obtained from surface matching procedure [76]. The two main advantages of the feature-based registration of lung CT images via currents are: no point correspondence is required and unified representation of curves and surfaces. The low dimensional geometrical features, such as curves and surfaces contain much fewer points compared to dense intensity images, thus feature-based registration can be more efficient. Moreover, in the framework of currents, dimensionality of image features may be reduced even more without decreasing registration accuracy [96].

In this chapter we apply the current-based registration method, pioneered by Glaunès et. al. [93] and further propagated by Durrleman [95, 97], to three feature sets: vessel centerlines, lung surface and combined set of centerlines and surface. We evaluated the registration methods on a set of 5 pairs of end exhalation and end inhalation phases of 4D-CT images with manually annotated landmarks.

3.2 Registration via Currents

This section describes how lung CT scans can be registered using the framework of currents, developed in [93, 98]. Firstly, Section 3.2.1 explains how curves and surfaces are represented via currents. Secondly, Section 3.2.2 describes how

anatomical lung structures, e.g., vessel tree and lung surfaces, were adapted to the framework of currents. Finally, Section 3.2.3 provides details of current-based registration of curves and surfaces.

3.2.1 Representation of curves and surfaces

In the framework of currents [93, 94, 97], geometrical shapes such as curves and surfaces are represented with a set of vectors. A current is encoded with a finite set of vectors attached to the specified positions. A curve C(x) can be defined with its tangent vector $\tau(x)$ at each position x. In a discrete setting, curve is considered as a set of piece-wise linear segments, where each segment is represented by its center point, tangential direction, and segment length. Similarly, a surface S(x), with a constructed mesh, is defined with the normal direction n(x), face center x and area. Both surfaces and curves are thus encoded into currents as a set of vectors. Geometrical shape in the framework of currents is defined in a weak form, as the action of the shape on a test vector field w from a space of possible vector fields W. The current of a curve $C(\omega)$ is defined by the path integral along the curve through the test vector field w,

$$C(\omega) = \int_C w(x)\tau(x)dx.$$
(3.1)

And the current of a surface $S(\omega)$ is defined by the flux of the vector field w trough the surface,

$$S(\omega) = \int_{S} w(x)n(x)dx.$$
(3.2)

The space W of test vector fields is a space of square integrable vector fields convolved with a Gaussian kernel with standard deviation λ_W [97, 94]. The norm of the current, $\mu(C)$, is defined in the dual space W^* , as the maximum action of the current among all possible test vector fields $||\mu(C)||_W = \sup_{||\omega||_W \leq 1} C(w)$. The scale λ_W controls matching accuracy, for example, curves or structures located within the scale size are considered similar, and their shapes should be matched with accuracy proportional to the scale size.

3.2.2 Lung structures as currents

In this chapter we used distinctive anatomical lung structures such as vessels and lung surfaces as features for registration. Figure 3.1a shows an example of segmented lung structures. The lung fields and vessels are segmented with the algorithm described in [87]. A sparse triangulation of the lung surfaces was computed via the marching cube algorithm [73]. For each face, the corresponding normals were computed and oriented to point outwards of the surface. Figure 3.1b shows an example of the constructed current for a lung surface.



(a) Example of segmented lung surface and lung vessel tree

(a) Example of segmented lung (b) Current corresponding to a lung surface.



(c) Current corresponding to a vessel tree centerlines.

Figure 3.1: Example of segmented lungs surface and vessel tree (a); triangulation of the lungs surface (black mesh) with the corresponding current (red vectors) (b); current corresponding to the vessel tree centerlines (red vectors) with a zoom-in (c).

Vessel tree was segmented as follows: a lung image was thresholded with a fixed intensity value $t_v = -600HU$, then a local analysis of Hessian matrix was performed in order to remove non-tube like structures. Large vessels segmented near the hilum area were omitted from the vessel tree segmentation. For more details on vessels segmentation algorithm we refer the reader to [87]. Centerlines were extracted from the segmented vessel tree using a 3D thinning algorithm [89].

The tangential direction of a centerline was computed via local principal component analysis. For each centerline point we extracted neighboring centerline points, applied PCA to the point cloud, and assigned the first principal component to the tangential direction at the centerline. For centerlines sufficiently far from vessel bifurcation and neighboring vessel, the principal direction points to a tangential direction of the centerline. For centerlines close to the bifurcation the principal direction points between the two splitting vessel centerlines. This is consistent with the framework of currents, were the action of each vessel direction results in a joint action at the bifurcation point. The orientation for the positive direction was set to point outwards from the center of the image. Figure 3.1c shows an example of the constructed current for a segmented vessel tree and a zoom-in into a bottom part of the image.

3.2.3 Current-based Image Registration

In this chapter, we combine the previous work on matching curves [94] and surfaces [93] via currents. The similarity measure between two curves C_f , C_m or two surfaces S_f , S_m is defined as the squared norm of the difference in μ for corresponding currents with respect to the test vector field $w \in W$:

$$E(C_f; C_m) = ||\mu(C_f) - \mu(\phi \cdot C_m)||_W^2, \qquad (3.3)$$

for fixed and moving curves C_f and C_m respectively. And

$$E(S_f; S_m) = ||\mu(S_f) - \mu(\phi \cdot S_m)||_W^2, \qquad (3.4)$$

for fixed and moving surfaces S_f and S_m respectively, where ϕ is a diffeomorphic transform function. Combining two similarity terms for curves (3.3), surfaces (3.4) and a regularisation term with trade-off coefficients $\gamma_C, \gamma_S, \gamma_{\phi}$ in a final cost function gives:

$$E(C_f, S_f; C_m, S_m) = \gamma_C ||\mu(C_f) - \mu(\phi \cdot C_m)||_W^2 + \gamma_S ||\mu(S_f) - \mu(\phi \cdot S_m)||_W^2 + \gamma_\phi \operatorname{Reg}(\phi).$$
(3.5)

Diffeomorphic transformation ϕ of curves and surfaces was modeled in the framework of large deformation diffeomorphic matching [92, 94], where deformation of each feature is defined by a velocity vector field $v_t = \phi'_t$. The smooth velocity field v_t is described via Gaussian kernel with standard deviation λ_V , where λ_V determines the typical scale of the deformations [97, 94]. To guarantee smoothness of the final diffeomorphism, we defined the regularisation term as in [97],

$$\operatorname{Reg}(\phi) = \int_0^1 ||v_t||_V^2 dt.$$
(3.6)

3.3 Experiments

In order to quantify the accuracy of the proposed registration method with a ground truth, we used images from a publicly available dataset [39]. For each image pair, 300 manually placed corresponding landmarks were provided [39].

Five pairs of images, where each pair consists of images extracted at end exhale and end inhale phases of 4D CT image, were used in our experiments. In-plane resolution of the images varied from 0.97×0.97 mm to 1.16×1.16 mm and slice thickness was 2.5 mm.

3.3.1 Parameter Settings

Vessel tree were segmented using the algorithm as in [87] with the intensity threshold -600 HU, ratio of Hessian eigenvalues was set to $m_1 = 0.75$, $m_2 = 0.5$. For every centerline point we extracted a neighboring centerline points from the cube neighborhood of $7 \times 7 \times 7$ voxels size and computed the principal direction of the centerlines. All the direction vectors were normalized to 1. Figure 3.1c shows an example of the extracted currents for vessel centerlines with a zoom-in to a lower part of the lungs. A regular surface triangulation was constructed with a marching cube algorithm with further simplification of the mesh [73]. Normal directions to each of the face were normalized to 1.

In our experiments, end inhale phase of 4D-CT image was registered to end exhale phase. The following internal parameters of image registration were selected manually. The accuracy of feature alignment λ_W was set to 5 mm for curves and 10 mm for surface features. The parameter λ_V for spatial variability of deformation velocity field was set to 25 mm for both types of features. The weight coefficients in the cost function (3.5) were set to $\gamma_C = 1$ for the curve matching term, $\gamma_S = 0.01$ for the surface matching term and $\gamma_{\phi} = 10^{-4}$ for the regularizer. The cost function was minimized with a standard gradient descent approach.

3.3.2 Results

We evaluated four registration methods, as follows: combined curve- and surfacebased registration with cost function (3.5); curve-based registration with cost function (3.3); surface-based registration with cost function (3.4); and a free-form B-Spline intensity-based method as in [29]. We compared registration accuracy of the four methods based on the alignment of 300 landmarks distributed uniformly in lung area, Figure 3.2b shows an example of the spatial distribution of landmarks within the lungs.

The overall accuracy of the image registration methods was defined as the mean Euclidean distance between landmarks, target registration error (TRE), in millimeters. The mean and the standard deviation of TRE for the four methods is reported in Table 3.3.2. We performed Wilcoxon rank-sum test on TRE distribution to compare the combined curve- and surface-based registration with the curve-based and surface-based methods individually. Results are reported in the Table 3.3.2. Box-plots in Figure 3.2a show the overall accuracy of the four image

Table 3.1: Registration error at the landmark positions in [mm] for the four registration methods. The mean (m) and the standard deviation (sd) are reported. Statistical comparison of combined curve- and surface-based registration method was performed against the surface-based and curve-based methods. The notations of statistical significance level are as follows: * corresponds to $p \leq 0.05$ and ^{ns} to p > 0.05. The most right column indicates percentage of landmarks, where the combined curve- and surface-based registration outperforms the intensity-based registration.

Image Registration Accuracy in mm $[m \pm sd]$						
Ν	Before	Combined	Surface	Curve	Intensity	%
1	3.89 ± 2.78	1.47 ± 0.72	$2.45 \pm 1.56^{*}$	$2.24 \pm 1.41^*$	1.23 ± 0.61	37.7
2	4.34 ± 3.90	2.19 ± 1.98	$3.63\pm2.94^*$	2.32 ± 2.06^{ns}	1.26 ± 0.67	39.0
3	6.94 ± 4.05	3.30 ± 3.05	$5.31\pm3.26^*$	$3.03\pm2.79^*$	1.86 ± 1.11	25.0
4	9.83 ± 4.86	3.34 ± 2.67	$5.98 \pm 3.74^{*}$	$5.28 \pm 4.52^*$	2.15 ± 1.48	36.0
5	7.48 ± 5.51	3.83 ± 3.54	$5.80 \pm 4.37^{*}$	$4.40\pm4.42^*$	2.32 ± 1.82	40.0
	All 5 cases					
	6.50 ± 4.83	2.83 ± 2.72	$4.63\pm3.58^*$	$3.45\pm3.48^*$	1.76 ± 1.31	35.5
Mdn	5.13	1.85	3.53	2.37	1.44	

registration methods on a complete set of landmarks over all five cases.

Correlation between TRE for the intensity-based and combined curve- and surface-based registration was $\rho = 0.5$, varying from 0.17 - 0.59 for the five cases. Overall, for 35.5% cases of landmarks the combined curve- and surface-based registration method performed better than intensity-based method.

3.4 Discussion

Figure 3.2a shows that the curve-based method alone provides good registration accuracy for the majority of landmarks. However, there are many outliers present with errors of up to 2.5 cm. Within the framework of currents, points located further than the typical scale of deformations λ_V are not affected by deformations of the features, which might cause landmarks distant to the vessel centerlines to be misaligned. Surface-based registration result in a slight overall improvement in TRE compare to the initial configuration. In contrast, incorporating both surfaces and curves into feature-based registration results in more accurate registration (1.85 mm) compared to both curve-based (2.37 mm) and surface-based (3.53 mm) methods.

The median of TRE for the combined curve- and surface-based registration was 1.85 mm compared to 1.44 mm for the intensity-based method. Several rea-

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(a) Box-plot of target registration errors.

(b) Distribution of landmarks.

sons may lead to larger TRE for the combined curve- and surface-based method, such as inconsistency in segmentations of vessels in the two images. Ambiguous segmentation of lung surface near the hilum may leads to large missregistration errors in this area. Figure 3.3b shows a difficult case in the data with irregular centerlines in the back of the lungs. Registration of lung images based on such geometrical structures as vessels centerlines and lung surfaces can be naturally improved by including airways and lung fissures into the presented framework.

In order to understand where are the main differences between the featurebased and intensity-based method, we visualized discrepancy between the two deformation fields in Figure 3.3a. For illustration purpose, we sparsely selected points, where the orientation between deformation vectors were above 60° and with the magnitude of discrepancy vectors more than 3 mm and plotted inside the lung area. Interestingly, the discrepancy between the feature- and intensity-based methods were localized.

We further investigate image slices located at the areas, where the discrepancy between the two methods was the largest (blue cut planes in Figure 3.3a). Figure 3.4 shows the difference image with the moving image subtracted from the fixed image for both registration methods. Overall, lung surfaces and small vessels were aligned more accurately with the feature-based registration method.

Another important component of currents is the length or the weight of the

Figure 3.2: Target registration errors (TRE) is shown in (a), as follows, before registration was applied (Initial), after surface-based (Suface), after curvebased (Curve), after combined curve- and surface-based (Combined) and after intensity-based registration (Intensity). Example (b) shows the spatial distribution of landmarks in the lungs. The landmarks, better aligned with the combined feature-based method are shown in red and with the intensity-based method in blue.

direction vector. For the task of registration of repeated lung CT images, the current for a small vessel could be given more weight than for a large vessel, leading to more accurate registration of small vessels. This is an important advantage of current-based registration over intensity-based method, where small vessels with low contrast to surrounding lung tissue have negligible impact on the overall cost function. In this chapter we used equal weights for all currents and normalized the length to 1.

On average, 35.5% of landmarks were aligned better with the curve- and surface-based registration. The low correlation coefficient (0.5) suggests that the two registration methods align landmarks differently and may be combined into a more robust registration method.



(b) Example of irregular current

(a) Deformation vectors for the combined curve- and surface-based (magenta) and intensity-based (green) methods methods

Figure 3.3: (a) An example of discrepancy in deformation fields between the feature-based and intensity-based registration methods. (b) An example of an ambigious current for the back of the lung.

3.5 Conclusion

In this chapter, a curve- and surface-based registration method is presented, where lung surfaces and vessel tree centerlines are built-in into the framework of current-based registration. Incorporating both centerlines and surfaces results in more accurate registration than curve- or surface-based registration method alone. The proposed combined curve- and surface-based registration method achieves slightly lower accuracy than intensity-based registration but for 35.5% of landmarks outperformed the intensity-based method. A natural extension of the presented work will be incorporating more anatomical lung structures, such as airways and fissures, to improve the feature-based method.

Results show that the proposed feature-based registration method is robust

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to inconsistent segmentation and outliers in segmented features and capable of handling imperfect segmentations. In applications where importance of different features varies, the prior weight of a feature may be encoded into the presented registration framework. Results suggest that a natural improvement of registration would be obtained by combining the feature- and intensity-based methods.



Intensity-based IR

(a)



(b)

Figure 3.4: Visual comparison of the combined feature-based and intensity-based registration methods. Slice cuts (a), (b) from the difference image between fixed and deformed image for the intensity- and combined feature-based registration methods were extracted on the same level as the plane cuts in Figure 3.3a. In general, the currents-based registration aligns the vessels and lung surface better, as can be seen in the areas indicated with the red circles and arrows.

Chapter 4

Lung CT Registration Combining Intensity, Curves and Surfaces

Take a chance and you may lose. Take not a chance and you have lost already.

— Søren Kierkegaard.

This chapter is based on the publication "Lung CT Registration Combining Intensity, Curves and Surfaces", Gorbunova V., Durrleman S., Lo P., Pennec X., de Bruijne M., in proceedings of IEEE International Symposium on Biomedial Imaging 2010.

4.1 Introduction

The ultimate goal of an image registration algorithm is to establish dense pointto-point correspondence between two images. Generally, registration of lung CT images is a difficult problem due to the possible large variation between the scans. Scans of the same patient taken at maximum inspiration, can have more than a liter difference in lung volume. The registration of end exhale and end inhale phases of 4D-CT lung images is an even more difficult problem due to the large and non-uniform deformations during the breathing cycle [53].

Image registration methods can be divided into two groups of methods: intensitybased and feature-based. Feature-based methods establish deformations based on low-dimensional features derived from the original images, e.g. points, curves or surfaces, while intensity-based methods consider intensity information over complete image. Several feature-based registration methods were developed for lung CT scans [37, 76, 25, 99]. However intensity-based registration methods are prevalent for the general purpose registration of lung CT scans [36, 48, 53, 52, 81, 29, 28, 39].

Intensity-based registration methods generally produce more accurate results [37, 24, 46]. Major drawback of the feature-based registration methods is the necessity to extract reliable features, e.g., landmark-based registration methods [39, 99, 25] require manually selected landmarks, and methods similar to the iterative closest point algorithm [37] require a good parameterization of the segmented structures. Recently, a current-based registration method was proposed for registration of surfaces [93] and curves [97, 94], where no point correspondence is required. We previously adapted the current-based registration for lung CT scans and showed that the accuracy of the current-based registration [46], although in 35 % of the landmarks, the current-based registration resulted in smaller target registration error.

While feature-based method can more accurately estimate deformation fields of the features, the intensity-based method can benefit from its results and improve the overall accuracy of alignment further away from the features. The direct combination of two different registration methods is usually not possible, particularly if the underlying deformation models are different. For example, in parametric non-rigid registration, deformation fields are commonly modeled with spline functions [36, 61, 44], while in non-parametric methods deformation fields are usually modeled using partial differential equations [62].

We propose a combined registration method, where the deformation field of an intensity-based registration is constrained with the results from a feature-based method. This constrained registration method is alternated with the featurebased registration method in an iterating scheme. A similar solution was previously proposed by Hellier et al. [100] where the deformation field between the corresponding sulcus lines was incorporated into the optic-flow based registration of the brain MRI scans. In the work [100], sulci in the two images were parameterized and deformations were obtained from corresponding points in the two curves. In contrast, in our feature-based registration curves and surfaces are represented without direct point correspondence, therefore consistent segmentation of the curves or surfaces in the two images is not required for the combined registration.

Our previous work [60] presented a combined registration method, where the intensity information was combined with the anatomical lung structures, e.g., vessel centerlines and lung surfaces. In this chapter we give a detailed description

of the proposed combined registration algorithm and evaluate performance on a publicly available set of 10 lung CT image pairs [39] with manually annotated landmarks.

4.2 Background and Previous Work

Generally, simple geometrical structures, e.g., points, curves and surfaces, which corresponds to distinct anatomical structures, are used as features in the featurebased registration. However more advanced features such as attribute vector [101] or filter response [102, 103] are also used in feature-based registration. Growing number of papers propose to combined geometrical features with intensities in registration framework [90, 104, 105, 106, 58, 100, 100, 76, 59, 103].

K. Rohr et al. [104] and H.J. Johnson et al. [90] proposed to combine landmarks with intensity based registration via an alternating approach. Minimization of the target registration error was alternated with the minimization of dissimilarity measure between images, thus achieving an optimal transformation.

Methods that combine curves and surfaces with intensities for registration purposes are common in magnetic resonance imaging field for analysis of brain MRI scans. Sulci and cortical surfaces were successfully combined with the intensity information [105, 58, 100, 106]. P. Cachier et al. [105] and P. Hellier [100] presented similar methods, where sulci were represented with a set of points and deformations between the corresponding sulci and intensity-based similarity measure were both incorporated into a cost function. D.L. Collins et al. [106] investigated different approach, where chamfer distance between the corresponding sulci was introduce into the registration framework. T. Liu et al. [58] proposed a multi-step registration algorithm where volumetric mapping was further improved by sequential surface alignment.

On contrary, combined feature-based and intensity-based registration of lung CT scans is not well investigated topic [76, 59, 103, 60, 107]. Recently, Li et al. [76] developed an image registration algorithm for lung CT images, where the intensity-based registration was improved with the subsequent bio-mechanical simulation of lung inflation obtained from lung surface deformations. The study [59] presents another hybrid method, where the registration algorithm integrates intensity-based and feature-based methods. The cost function incorporates difference in intensities and difference in the distances to the annotated surfaces. Similar approach was proposed in [107], where cost function incorporates dissimilarity between the original images and between the vessel probability images. A hybrid approach where features of lung CT scans were determined from an eigenvalue analysis and further considered along with the intensities in the registration procedure [103]. In all the above studies, results showed improvement of the combined registration methods compare to the registration methods based

on the intensity alone.

4.3 Method

Section 4.3.1 briefly repeats the feature-based registration method from the Chapter 3. The non-rigid intensity-based registration method from the Chapter 2 is described in the Section 4.3.2. Detailed description of the proposed registration, where the intensity is constrained with the deformations of anatomical lung structures, is given in the Section 4.3.3. Finally, the details of an iterating scheme, where the combined registration is alternated with the feature-based registration is described in the Section 4.3.4.

4.3.1 Current-based Registration

In our previous work, we developed a feature-based registration, where vessel centerlines and lung surfaces, were used to establish spatial correspondence between lung CT scans [46]. Both vessel centerlines and lung surfaces were represented in a framework of currents and aligned using the metric on currents. The current μ for a vessel centerline C is represented by tangential vectors attached to the centerline points, and for a triangulated surface S it is represented by normal directions attached to the centers of each face. Figure 4.1a show an example of the currents for the vessel centerlines, and the lung surfaces is shown in Figure 4.1b.

Norms of a currents for curves and surfaces, $\mu(C)$ and $\mu(S)$, are defined via a path integral along the curve or a flux integral through the surface [94]. The cost function between anatomical lung structures in a fixed image C_f and S_f and a moving image C_m and S_m is defined as a weighted sum of the similarity measures between currents for the vessel centerlines C_f and C_m , the similarity between currents for surfaces the S_f and S_m , and a regularization term:

$$E(C_f, S_f; C_m, S_m) = \gamma_C ||\mu(C_f) - \mu(\phi \cdot C_m)||_W^2 + \gamma_S ||\mu(S_f) - \mu(\phi \cdot S_m)||_W^2 + \gamma_\phi \int_0^1 ||v_t||_V^2 dt.$$
(4.1)

Diffeomorphic transformation ϕ of curves and surfaces was modeled in the framework of large deformation diffeomorphic matching [94], where deformation of each feature point is defined by a velocity vector field $v_t = \phi'_t$. The smooth velocity field v_t is described via a Gaussian kernel with standard deviation λ_V , where λ_V determines the typical scale of the deformations [97]. The smoothness of the currents is determined by the parameter λ_W [97].

4.3.2 Intensity-based Registration via B-Splines

In this chapter we used a multi-resolution B-Spline image registration framework [61] for the intensity-based registration. First, lung regions were extracted



Figure 4.1: Example of currents constructed for the segmented vessel centerlines (a) and the lung surfaces (b), both seen from the side.

from the CT images and the background value was set to 0 HU. Images were aligned with affine transform T_A . Subsequently, a series of N B-Spline transforms $T_{\text{B-Spline}}^{i=1..N}$ with decreasing grid size was applied to the affinely registered images. Thus, the final deformation is a composition of the affine transform and N levels of the B-Spline transforms:

$$T_{\text{final}}(\mathbf{x}) = T_{\text{B-Spline}}^{N} \circ \dots \circ T_{\text{B-Spline}}^{1} \circ T_{A}(\mathbf{x}), \qquad (4.2)$$

where \mathbf{x} is a point in the fixed image domain Ω_f . We use the sum of squared intensity differences as the similarity measure between the images,

$$E_{int}(I_f, I_m; T) = \frac{1}{|\Omega_f|} \int_{\Omega} [I_f(\mathbf{x}) - I_m(T(\mathbf{x}))]^2 d\mathbf{x}, \qquad (4.3)$$

where $I_f(\mathbf{x})$ is the fixed image, defined in the fixed image domain Ω_f , $I_m(\mathbf{y})$ is the moving image, defined in the moving image domain Ω_m . After each level of transform the moving image $I_m(\mathbf{y})$, where $\mathbf{y} = T(\mathbf{x})$, is deformed with the sum of the obtained transforms and interpolated using linear interpolation.

4.3.3 Constrained Registration

We propose to constrain the intensity-based registration of Section 4.3.2 with the deformation field obtained from the current-based registration of Section 4.3.1. We constrain B-Spline deformation field $\vec{D}_{\text{B-Spline}}(\mathbf{x})$ to match the given deformation field $\vec{D}_{\text{curr}}(\mathbf{x})$ by minimizing the \mathcal{L}_2 distance between the deformations. Since the current-based registration uses anatomical lung features to establish the correspondence, the deformation field in locations close to the extracted features is expected to be more reliable than further away from the features. Thus, we propose to incorporate a spatially varying weight $w(\mathbf{x}) \in [0; 1], \mathbf{x} \in \Omega_f$ into the constraint between the deformation fields, which defines the trade off between

matching intensity and deformations for every voxel \mathbf{x} . The combined cost function then consists of the sum of squared intensity differences similarity function and constraint on the deformation field:

$$E(I_f, I_m; T) = E_{int} + \lambda E_{def} =$$

$$= \frac{1}{|\Omega|} \int_{\Omega} (1 - w(\mathbf{x})) \left[I_f(\mathbf{x}) - I_m(T(\mathbf{x})) \right]^2 d\mathbf{x}$$

$$+ \frac{\lambda}{|\Omega|} \int_{\Omega} w(\mathbf{x}) ||\vec{D}_{\text{B-Spline}}(\mathbf{x}) - \vec{D}_{\text{constr}}(\mathbf{x})||^2 d\mathbf{x}, \qquad (4.4)$$

where the constraining deformation field is $\vec{D}_{\text{constr}}(\mathbf{x}) = \vec{D}_{\text{curr}}(\mathbf{x})$ and the coefficient λ compensates for the difference in units of the two terms. The deformation field $\vec{D}_{\text{B-Spline}}(\mathbf{x})$ is a vector field defined as $\vec{D}_{\text{B-Spline}}(\mathbf{x}) = T(\mathbf{x}) - \mathbf{x}$. Using vector notation, the gradient of the cost function (4.4) can be computed explicitly:

$$\mathcal{D}_{\mathbf{a}}E(I_f, I_m; T) = -\frac{2}{|\Omega|} \int_{\Omega} (1 - w(\mathbf{x})) \left[I_f(\mathbf{x}) - I_m(T(\mathbf{x})) \right] \cdot \left[\mathcal{D}_{\mathbf{x}} I_m \ \mathcal{D}_{\mathbf{a}} T \right] d\mathbf{x} -\frac{2\lambda}{|\Omega|} \int_{\Omega} w(\mathbf{x}) (\vec{D}_{\text{B-Spline}}(\mathbf{x}) - \vec{D}_{\text{curr}}(\mathbf{x}))^T \mathcal{D}_{\mathbf{a}} T d\mathbf{x}.$$
(4.5)

Where the symbol $\mathcal{D}_{\mathbf{x}}$ denotes the spatial gradient vector operator $\mathcal{D}_{\mathbf{x}}(\cdot) = (\frac{\partial}{\partial x_1}(\cdot); \frac{\partial}{\partial x_2}(\cdot); \frac{\partial}{\partial x_3}(\cdot))$, and the symbol $\mathcal{D}_{\mathbf{a}}$ denotes the gradient vector operator with respect to the transform coefficients $\mathcal{D}_{\mathbf{a}}(\cdot) = (\frac{\partial}{\partial a_1}(\cdot); ... \frac{\partial}{\partial a_N}(\cdot))$.

In the multi-level framework of the intensity-based image registration described in Section 4.3.2, each level of the transform is constrained separately. The initial affine transform is not constrained, and for the subsequent N levels of the B-Spline transform the deformation field at a given point is constrained with the remaining deformation field, as follows:

$$\vec{D}_{\text{constr}}^{\text{level}}(\mathbf{x}) = \vec{D}_{\text{curr}}(\mathbf{x}) - \vec{D}_{\text{aff}}(\mathbf{x}) - \sum_{i=1}^{\text{level-1}} \vec{D}_{\text{B-Spline}}^{i}(\mathbf{x}).$$
(4.6)

4.3.4 Iterative Scheme

The described combined registration method is naturally extended to an iterative approach where registration alternates between the combined method from the Section 4.3.3 and the current-based registration from Section 4.3.1. The interaction of the two registration algorithm presented in the Figure 4.2. After a level *i* of the combined registration, the vessel centerlines currents $\mu(C_f)$ and lung surfaces currents $\mu(S_f)$ extracted from the fixed image are deformed with the obtained deformation field $\vec{D}_{\text{B-Spline}}^i$ and a new iteration of the current-based registration of Equation (4.1) restarted on the deformed currents, defined as:

$$\mu^{i+1}(C_f) = \mu(C_f \cdot \vec{D}_{\text{B-Spline}}^i)$$
(4.7)

$$\mu^{i+1}(S_f) = \mu(S_f \cdot \vec{D}_{\text{B-Spline}}^i) \tag{4.8}$$



Figure 4.2: The workflow of the iterative image registration. The combined registration from Section 4.3.3 is applied between the original fixed image $I_f(\mathbf{x})$ and the original moving image $I_m(\mathbf{y})$ with the constrain on the deformation field $\vec{D}_{\text{constr}}(\mathbf{x})$. The subsequent current-based registration from Section 4.3.1 is applied between the deformed currents of the fixed image $\mu(C_f)$, $\mu(S_f)$ and the currents of the moving image $\mu(C_m)$, $\mu(S_m)$. Detailed description of the algorithm is given in Algorithm 4.1.

Since the current is a set of vector points, the deformed current is obtained from the deformation of the start and the end points of each vector. Details on the initialisation and step-by-step description of the iterative process is summarised in Algorithm(4.1). Using the described scheme we can iterate the current-based and the combined registration gradually improving the result.

4.4 Experiments

4.4.1 Data

We conducted experiments on ten publicly available image pairs extracted at the end exhale and end inhale phases of 4D-CT scans [39]. The study also provides 300 manually placed landmarks for each image pair. The landmarks were uniformly distributed over the lungs. In-plane resolution of the images varied from 0.97×0.97 mm to 1.16×1.16 mm and slice thickness was 2.5 mm. For each pair, the image extracted at end inhale phase of 4D CT image was registered to the image extracted at end exhale phase.

Algorithm 4.1: Algorithm describes the iterating scheme illustrated in Figure 4.2.

Problem Statement: For every point $\mathbf{x} \in \Omega_f$ find the corresponding point $\mathbf{y} = \mathbf{x} + \vec{D}(\mathbf{x})$ in the moving image domain Ω_m .

Initialization: Initial constraining deformation field $\vec{D}_{constr}^0 = 0$, the weight
image $w(\mathbf{x}) = 0$, transform parameters $\mathbf{c}^0 = 0$ and
the fixed image currents $\mu^0(C_f) = \mu(C_f), \ \mu^0(S_f) = \mu(S_f).$
for $i = 0N$ do
1: Run combined image registration with the constraining deformation
field $\vec{D}_{\text{constr}}^{i}$ and initial guess on transform coefficients \mathbf{c}_{ini}^{i} ,
2: Compute the deformation field $\vec{D}_{\text{B-Spline}}^{i+1}$ and deform the fixed image
currents $\mu^{i+1}(C_f, S_f) = \mu(C_f \cdot \vec{D}^i_{\text{B-Spline}}; S_f \cdot \vec{D}^i_{\text{B-Spline}}),$
3: Run current-based image registration between $\mu(C_m, S_m)$ and
$\mu^{i+1}(C_f, S_f)$
4: Update the deformation field $\vec{D}_{\text{constr}}^{i+1} = \vec{D}_{\text{constr}}^i + \vec{D}_{\text{B-Spline}}^{i+1}$ and
the transform coefficients $\mathbf{c}_{ini}^{i+1} = \mathbf{c}_{converged}^{i}$.
end for

4.4.2 Setup of the Current-based Registration

Lung fields and main bronchi were segmented as described in [108]. From the segmented lung regions, the lung surfaces triangulation were constructed using the marching cube algorithm and further simplified in order to decrease the number of faces [73]. The normal directions were attached to the center of each facet, the length was normalized to 1 mm and the orientation was set to point outwards from the lung surface. Figure 4.1b shows an example of the constructed current for the lung surfaces.

Vessel tree was segmented using the algorithm as in [87] with the intensity threshold -600 HU. The internal parameters of the segmentation algorithm such as ratios of the Hessian eigenvalues were set to $m_1 = 0.75$ and $m_2 = 0.5$. Vessel centerlines were extracted using a 3D thinning algorithm [89]. Finally, tangential directions of the vessel centerlines were computed via local principal component analysis in a $7 \times 7 \times 7$ voxel size cube. The orientation and the length of the tangential direction is important in the current-based registration, therefore we normalized the length of the first principal vector to 1 mm and the orientation was set to point outwards from the image center. Figure 4.1a shows an example of the constructed currents for the vessel tree segmented from the right lung.

We applied the current-based registration from Section 4.3.1 to register vessel trees and lung surfaces. The internal parameters of the current-based registration were set to $\lambda_W = 5$ mm for the vessel currents, $\lambda_W = 10$ mm for the surface