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Patch-based Lung Ventilation Estimation using Multi-layer Supervoxels

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Abstract

Patch-based approaches have received substantial attention over the recent years in medical imaging. One of their potential applications may be to provide more anatomically consistent ventilation maps estimated on dynamic lung CT. An assessment of regional lung function may act as a guide for radiotherapy, ensuring a more accurate treatment plan. This in turn, could spare well-functioning parts of the lungs. We present a novel method for lung ventilation estimation from dynamic lung CT imaging, combining a supervoxel-based image representation with deformations estimated during deformable image registration, performed between peak breathing phases. For this we propose a method that tracks changes of the intensity of previously extracted supervoxels. For the evaluation of the method we calculate correlation of the estimated ventilation maps with static ventilation images.

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acquired from hyperpolarized Xenon129 MRI. We also investigate the influence of different image registration methods used to estimate deformations between the peak breathing phases in the dynamic CT imaging. We show that our method performs favorably to other ventilation estimation methods commonly used in the field, independently of the image registration method applied to dynamic CT. Due to the patch-based approach of our method, it may be physiologically more consistent with lung anatomy than previous methods relying on voxel-wise relationships. In our method the ventilation is estimated for supervoxels, which tend to group spatially close voxels with similar intensity values. The proposed method was evaluated on a dataset consisting of three lung cancer patients undergoing radiotherapy treatment, and this resulted in a correlation of 0.485 with XeMRI ventilation images, compared with 0.393 for the intensity-based approach, 0.231 for the Jacobian-based method and 0.386 for the Hounsfield units averaging method, on average. Within the limitation of the small number of cases analyzed, results suggest that the presented technique may be advantageous for CT-based ventilation estimation. The results showing higher values of correlation of the proposed method demonstrate the potential of our method to more accurately mimic the lung physiology.

**Keywords:** lung ventilation estimation, supervoxels, XeMRI ventilation, deformable registration

### 1. Introduction

Patch-based methods have become an essential tool in many fields of computer vision and medical imaging. In computer vision they are used for
object localization and class segmentation [1], human pose [2] and depth estimation [3, 4], or to generate image descriptors [5, 6, 7]. There has also been a surge of growth of their application in medical imaging. They have been successfully applied to enhance image segmentation [8, 9], as well as to tumor segmentation [10, 11, 12] or analysis of its texture [13]. For lung image analysis, they have been applied, for instance, to enhance resolution of 4D computed tomography (4DCT) [14]. Other applications are patch-based descriptors for image similarity measure [15, 16] and patch-based image registration approaches [17, 18, 19].

A potential application of patch-based methods is to estimate regional ventilation of the lungs based on 4DCT. This is an important application, as pulmonary-related diseases are among the leading causes of death worldwide [20]. Lung cancer is the most common cause of cancer death and the second most commonly diagnosed cancer type in both male and female populations [21], and Chronic Obstructive Pulmonary Disease (COPD) is responsible for nearly twice as many deaths as breast cancer [20]. Tests measuring overall lung condition may not be specific enough to help localize and confront these challenging diseases [22]. The gold standard test for pulmonary function is the spirometry technique, which evaluates global lung function by measuring the volume and speed of air during inhalation and exhalation. Although this method is cheap, fast, and widely used as a screening tool [23], it lacks regional lung evaluation and thus cannot be used for precision medicine such as individualized radiotherapy planning [24]. Assessment of the regional lung functionality has the potential to provide more accurate radiotherapy treatment [25], which could spare well-functioning parts of the lungs and be
used for follow up to evaluate the treatment effectiveness.

The estimation of ventilation surrogates based on CT images is an active field of research. In [26], for instance the Dice overlap of percentage ventilation volumes between 4DCT originating ventilation estimates and $^{3}$He MRI was investigated, and no significant difference was found. That study supports the claim that well-ventilated regions in 4DCT-based ventilation surrogates and $^{3}$He MRI are in agreement. A lobar oriented analysis of lung ventilation was presented in [27], where the authors compared CT-based ventilation surrogates with $^{3}$He MRI for asthma patients. The authors found agreement between the investigated ventilation imaging methods. An interesting study was presented in [28], where, apart from investigating the correlation between different CT-based ventilation estimation techniques and hyperpolarized gas MRI ventilation images, the correlation between $^{3}$He MRI and $^{129}$Xe MRI was evaluated. They found significantly lower correlation between CT originating ventilation surrogates and hyperpolarized gas MRI ventilation maps than between $^{3}$He MRI and $^{129}$Xe MRI. In order to search for the best indicator of lung function, the authors of [29] investigated correlation between ventilation estimated from $^{129}$Xe MRI and the quantity of gas transferred to red blood cells (RBCs). Their initial conclusion was that $^{129}$Xe MRI ventilation may not be the optimal measure of the true regional lung function. Despite the amount of work done in the field, there is still scope for further research in the methods dedicated for estimating ventilation from CT images.
1.1. Aims

The aim of this work is to introduce a patch-based ventilation estimation method and perform its evaluation, comparing its results with magnetic resonance imaging with hyperpolarized $^{129}$Xe as an inhalable contrast agent (XeMRI). We run a number of experiments to investigate the parameter setting and robustness of the method. The original idea and preliminary results were presented in [30]. This paper has been extended in the following way:

1. We present, in detail, the proposed method for regional ventilation estimation, including a thorough investigation of the influence of relevant parameters.
2. We show the performance of our approach for different image registration methods.
3. We provide a quantitative comparison between state-of-the-art methods for lung ventilation estimation and the proposed method.
4. We correlate our results with XeMRI using the developed registration approach between proton density MRI (pMRI) and CT, which we explain in detail.

The remaining part of this section is organized as follows: in Sec. 1.2 we present lung ventilation imaging methods based on MRI and CT. Subsequently, in Sec. 1.3 we discuss lung image registration when applied to lung CT. We follow this by introducing lung ventilation estimation techniques based on 4DCT in Sec. 1.4.
1.2. Lung Ventilation Imaging

Lung ventilation imaging allows insight into local lung function. Most of the lung ventilation imaging techniques require the use of ionizing imaging methods and radioactive tracers, such as Single Photon Emission Computed Tomography (SPECT) [31] or Positron Emission Tomography (PET) [32]. A lung function imaging technique that has received substantial attention in the field is hyperpolarized noble gas MRI [33, 34]. Its non-ionizing nature makes it a promising technique for imaging ventilation, perfusion and gas transfer within the lungs [34]. In the static approach of this method, the patient breathes in a fixed volume of hyperpolarized noble gas and images are acquired during breath hold. Static hyperpolarized XeMRI provides images with direct visualization of the distribution of the inhaled gas in the patient’s lungs. Compared with the aforementioned lung functional imaging techniques, XeMRI is acquired during a single breath-hold. To allow for the localization of ventilation images with respect to the patient anatomy, pMRI is acquired immediately before XeMRI acquisition. As an extension to the static XeMRI lung ventilation imaging, dynamic XeMRI has been recently proposed [35]. In this method several volumetric images are acquired over a number of breathing cycles in a single imaging. Currently, the main drawback of the technique is its accessibility, which is limited to a number of imaging centers in the world.

4DCT, on the other hand, is a structural imaging technique routinely used for radiotherapy planning, where images are acquired during free breathing under spirometry control. It can be used to estimate lung ventilation maps, based on the results of the registration between peak-exhale and peak-inhale
breathing phase volumes. 4DCT based ventilation methods can be roughly
classified into those, which rely on the value of the determinant of the Jaco-
bian matrix of the deformations to estimate the lung volume change [36, 37],
methods tracking the changes in the intensity of the lungs quantified in
Hounsfield units (HU) [38, 24], and those based on averaging a product of
air and tissue fraction across all breathing phases [39]. Changes in tissue
attenuation correspond to variations in tissue density and originate from fill-
ing the lungs with air. The Jacobian-based and intensity tracking methods
require estimation of the deformation field between peak breathing phases
from 4DCT, performed by deformable image registration. In contrast, the
averaging method [39] does not need to estimate deformations.

1.3. Lung Image Registration

The task of deformable image registration is to bring two or more images
into alignment, based on a specified similarity measure. To ensure not only
a perfect match for each voxel but also plausibility of the estimated defor-
mation field, a regularization is required. This can be done, for instance, by
incorporating it into a transformation model, such as Free Form Deforma-
tions (FFDs) with B-Splines [40], by adding an additional regularization term
to the optimization [41, 42], or by incorporating sparse key-points matching
[43].

To investigate the robustness of the proposed ventilation estimation method
on the applied image registration method, we used a number of different ap-
proaches: the deeds method [44], classic demons method [45], its extended
version applying bilateral filtering (BLF) [41], and supervoxel-based graph
cuts [46]. The aim of this experiment is to evaluate if the obtained patters
in the results are independent of the applied image registration method to estimate deformations, rather than to determine which of the methods is the most suitable for this application.

In the first method [44] the optimization problem is posed on a minimum spanning tree (MST) extracted from a graph created over a regular grid. Each node in the graph represents a cubic patch of voxels. The authors used a belief propagation as the optimisation technique, which for a MST stated problem can find the global minimum. The final deformation field is achieved by using B-spline interpolation of the resulting sparse optimization outcome. We will refer to this method as: deeds.

The second investigated method is the well established demons method [45, 47]. In the primary work [45], the optimization is performed in an alternate way, in which finding the best displacement at each iteration for every voxel is followed by a filtering of the estimated displacement field, where the filtering works as a regularization. The method was later extended to preserve diffeomorphism [47]. The authors used Gaussian filtering, which did not take into account the discontinuities appearing at the borders of the lungs. Such a limitation was shown to result in the underestimation of displacements near the borders of the lungs. We will refer to this method as demons.

The third evaluated method is an extension of the previous. In [41], the authors addressed the problem of preservation of discontinuities at the borders of the lungs, called sliding motion, by introducing an additional filtering kernel in the form of bilateral filtering (BLF) [48]. The method showed an improvement in accuracy of the results, as well as more anatomically plau-
sible deformations, especially within problematic lung regions. We will refer to this method as demons BLF.

The fourth method [46] applies graph cuts [49] as an optimization method over the images previously clustered into supervoxels. In the optimization step for each of the supervoxels the best displacement is found from a predefined set of allowed displacements. As a result of this step we obtain a deformation estimated for each of the supervoxels. A direct application of this displacement to all of the voxels belonging to the supervoxel might result in foldings at the borders of supervoxels that have different deformations and thus physiologically implausible deformations. This issue has been addressed by applying guided image filtering [50], akin to [51]. The resulting displacement field remains smooth in the homogeneous regions, at the same time preserving discontinuities at the borders of the organs, such as those between the lungs and rib cage or lungs and diaphragm. In the following part of the paper this method will be referred to as supervoxel graph cuts.

All of the methods have shown good performance in a publicly available Dir-Lab dataset [52], with 300 manually annotated landmarks provided for evaluation purpose. The deeds method resulted in Target Registration Error (TRE) on the dataset of 1.43mm, for Demons and their BLF extension TREs of 2.35mm and 1.95mm were measured, respectively, and for the supervoxel graph cuts TRE was 1.16mm. All registration methods used for the evaluation of our new method for ventilation estimation were optimized using Dir-Lab, and all of them were optimized by their authors to get the best TRE on Dir-Lab. We have applied them with the provided parameters. These image registration method parameters were set completely indepen-
dent of our testing dataset. There are other lung image registration methods [53, 54] and even approaches dedicated for lung mass/tissue preserving during the alignment process [55, 56, 57]. These methods, though presenting an interesting approach for enhancing similarity measure, resulted in moderate performance when evaluated on the Dir-Lab dataset. Our choice covers main registration categories in terms of optimization, namely: discrete, continuous, and hybrid.

1.4. Ventilation Estimation from 4DCT

There are several methods to estimate ventilation from 4DCT. In this section we discuss the existing approaches for this task, starting from those requiring estimation of the displacement field. These methods can be divided into intensity-based [24, 38] and Jacobian-based [36, 37] methods. We then present the method which applies the relation between air and tissue fraction and does not require image registration [39].

Intensity/Density Change Ventilation Estimation Method: One of the approaches for ventilation estimation from 4DCT is to track changes in lung intensity throughout the breathing process. As CT intensity is directly related to the tissue density, it reflects the changes originating from filling the lungs with air. Following [24, 58], the ventilation is estimated for the full exhale phase:

\[
Vent_{Dens}^{exh}(x) = \left( \frac{HU_{exh}(x) \ast G_{k1} - HU_{inh}(x + u_{inh}) \ast G_{k1}}{HU_{inh}(x + u_{inh}) \ast G_{k1} + 1000} \right) \ast G_{k2},
\]  

(1)

with \( HU_{exh}(x + u_{exh}) \) being an intensity value expressed in Hounsfield units (HU) for a voxel at spatial position \( x \) of the peak exhale phase image warped
towards the peak inhale phase image by the displacement field $u_{inh}$. Similarly, $HU_{inh}(x)$ represents intensity value of peak inhale image for the same voxel $x$. $G_{k1}, G_{k2}$ are Gaussian kernels used for smoothing and convolved (denoted by $*$ in the equation) with the images. Some researchers substituted Gaussian kernels with box filter kernels, [59], or with median filter kernels, [28, 60]. In our study we followed the original formulations of [24, 58], therefore, we will subsequently refer to the Gaussian filtering. The investigation of the influence of the applied filtering methods was out of the scope of this work. In [61] the authors investigated the reproducibility of the intensity-based approach for a number of different parameters and cases. All the image intensities are given in HU.

_Jacobian-based Method:_ Local lung volume change can be used as a measure of lung ventilation [36]. The determinant of the Jacobian of deformations estimated by deformable registration between different breathing phases is.

$$Vent_{JAC}(x) = \left| \begin{array}{ccc}
1 + \frac{\partial u_x(x)}{\partial x} & \frac{\partial u_x(x)}{\partial y} & \frac{\partial u_x(x)}{\partial z} \\
\frac{\partial u_y(x)}{\partial x} & 1 + \frac{\partial u_y(x)}{\partial y} & \frac{\partial u_y(x)}{\partial z} \\
\frac{\partial u_z(x)}{\partial x} & \frac{\partial u_z(x)}{\partial y} & 1 + \frac{\partial u_z(x)}{\partial z}
\end{array} \right|$$

(2)

with $u_x, u_y, u_z$ being the deformation fields estimated in $x, y$ and $z$ directions respectively. The determinant of the Jacobian of the deformations taking values between 0 and 1 indicate for shrinking the lung volume, values of 1 mean no volume change for the region and values over 1 indicate volume expansion calculated for a spatial location $x$. Such an approach has been applied in [37], where XeCT-based ventilation volumes were compared with the ventilation estimated based on the determinant of the Jacobian. Recently a sensitivity analysis of the determinant of the Jacobian for lung cancer treatment
planning has been presented [62]. The reproducibility of the Jacobian-based ventilation has been investigated in [63]. It has been shown that the method correlates well with lung function in emphysema patients [58].

**Air/tissue Fraction Averaging Method:** In contrast to previously presented methods, the HU-based method [39] does not require image registration between breathing phases. Instead of performing image registration between full inhale and full exhale phases, the authors propose to estimate lung ventilation in terms of a product of air and tissue fractions density calculated locally for all of the breathing phases and subsequently averaged across them:

\[
V_{\text{vent}}(x) = \frac{1}{N} \sum_{\phi=1}^{N} V_{\phi}(x)
\]

\[
V_{\phi}(x) = \begin{cases} 
\frac{\text{HU}_{\phi}(x)}{-1000} \times \frac{\text{HU}_{\phi}(x)+1000}{1000} & \text{for } x \in L(\phi) \\
0 & \text{for } x \notin L(\phi)
\end{cases}
\]

where \( \phi \) is a current number of the breathing phase in 4DCT with \( N \) being the total number of breathing phases, and \( L \) is the mask of the lungs delineated from the peak inhale phase. The method was reported to have good correlation with Galligas PET for normal patients control group but it failed to achieve the same accuracy for individuals with severe ventilation distortions. Such behavior could be expected due to the estimation of the ventilation based on a relation between air and tissue fraction for a single phase. A clearly problematic case is the detection and evaluation of the air trapped in the lungs for patients with severe Chronic Obstructive Pulmonary Disease (COPD).

The remaining part of this paper is organized in the following way: in
Sec. 2 we introduce our proposed method for estimating ventilation in a patch-based manner. The results of the proposed experiments are presented is Sec. 3, which are finally discussed and concluded in Sec. 4.

2. Methods

In this section we present the proposed supervoxel-based lung ventilation estimation method. We introduce the image clustering method in Sec. 2.1, as well as explain how we apply it to the proposed method in Sec. 2.2. A work-flow diagram presenting the method is shown in Fig. 1. Finally in Sec. 2.3 we present the proposed image registration framework in which we bring the estimated ventilation maps from 4DCT to align with XeMRI ventilation images.

2.1. Supervoxel clustering

One of the approaches for patch-based methods is supervoxel-based image representation. Supervoxel-based image clustering groups voxels that are spatially close and visually similar into larger structures. They have become the building blocks for many applications in computer vision and medical image analysis. In our formulation, we apply Simple Linear Iterative Clustering (SLIC) [64] as a clustering method, due to its speed of performance and direct control over the number of extracted supervoxels and supervoxel compactness. The SLIC method is designed to extract $k$ approximately equally-sized supervoxels. Initially, seeds of the supervoxels are placed on a regular grid at intervals $S = \sqrt{M/k}$ voxels apart, with $M$ being the total number of voxels in the image. In the original work by Achanta [64], the method was proposed for 2D images, whereas here we apply it to 3D supervoxels. The positions of
Figure 1: The diagram shows the work-flow of the proposed approach for patch-based lung ventilation estimation. We start by performing deformable image registration between peak breathing phase volumes. We follow that by clustering the peak exhale image into a number of supervoxels. We extract a number of layers of supervoxels, each with slightly different initial parameters, which is depicted in the figure by multiple boxes for the current and following steps. After that we apply the previously estimated deformations to the extracted supervoxels. The original supervoxels extracted from the peak exhale image are interpolated and labeled using the same color. For the initial position of the supervoxels their mean intensity values are calculated. We map the warped supervoxels over the peak inhale image to calculate changes in their mean intensity between the mapping over the peak exhale and peak inhale breathing phase volumes. Finally we average the results obtained for all the supervoxel layers. Contours in images show lungs, ribs and main airways position. For illustrative purposes the supervoxels are extracted from a 2D image.
the centers are then corrected based on the gradients of the image to prevent their placement on image edges or at a noisy voxel. Individual voxels are assigned to the closest cluster based on the distance:

\[ \mathcal{Y} = \sqrt{(d_e)^2 + \left(\frac{d_I}{S}\right)^2} m^2, \]  

(5)

where \( m \) is a parameter setting the compactness of supervoxels, the distance \( \mathcal{Y} \) is an iteratively calculated combination of Euclidean distance \( d_e = \|x - c\| \)
and the intensity-based similarity is \( d_I = \|I(x) - I(c)\| \), where \( x \) is voxel position and \( c \) are cluster centers updated after each iteration.

2.2. Supervoxel tracking for ventilation estimation

The existing methods [24, 36, 39, 58] for estimating ventilation from 4DCT take the structural relationship between voxels into account mainly at the image registration step or derivatives calculation. In this work we apply the proposed patch-based method, which additionally addresses structural relationship directly and estimates ventilation for larger, spatially and visually consistent regions. Such an approach may be more meaningful from an anatomical point of view. The lungs are divided into right and left lungs, which are further separated into lobes, while each lobe consists of a number of segments. All of them are supplied with separate airways which form a tree-like structure with no additional interconnections between the subtrees. Therefore, the ventilation of the neighboring lobes or sections supplied by different branches of the airway tree may differ. Supervoxels have the potential to cluster anatomically consistent lung regions and, therefore, ventilation surrogates would not be estimated across anatomical borders of the lungs.
In most of the previous studies ventilation images were estimated for peak exhale [58]. However in our work we used the peak inhale breathing phase as a reference, as the difference in the volume of the lungs between pMRI and CT was then the smallest. Such an approach should result in smaller deformations applied during pMRI to CT registration and, therefore more accurate results of the registration. A similar approach has been recently applied in [28] to address the same challenges. We then formulate an estimate of the ventilation for peak inhale as follows:

$$V_{vent}^{inh}(x) = \left( \frac{HU_{exh}(x + u_{exh}) \ast G_{k1} - HU_{inh}(x) \ast G_{k1}}{HU_{inh}(x) \ast G_{k1} + 1000} \right) \ast G_{k2}$$

with $HU_{exh}(x)$ denoting the lung intensity value from peak exhale breathing phase image for voxel position $x$ and $HU_{inh}(x + u_{inh})$ lung intensity value from peak inhale breathing phase image for the same voxel moved by displacement field $u_{inh}$ and $G_{k1}, G_{k2}$ are Gaussian kernels used for smoothing and convolved with the images. All the image intensities are given in HU.

We start by extracting supervoxels from the peak exhale breathing phase image and then calculate their mean intensities. Subsequently, we apply the deformations originating from image registration between peak exhale and peak inhale breathing volumes to the extracted supervoxels. In this way we map the same regions, represented by supervoxels, from the peak exhale to the peak inhale image (see Fig. 1). We recalculate mean intensities of the transformed supervoxels, this time over the peak inhale image. Then we apply this approach to the method described above, thus estimating ventilation for supervoxels rather than for each individual voxel:
Figure 2: Comparison of the estimated ventilation maps using different methods for Patient 2 in coronal view. The results are presented for the supervoxel graph cuts image registration method. Lung contours extracted from the CT image are propagated onto ventilation images.

\[
Vent_{SLIC}(s) = \frac{HU_{exh}(s + u_{exh}) - HU_{inh}(s)}{HU_{inh}(s) + 1000},
\]

where \(HU_{inh}(s)\) is the mean intensity of a supervoxel \(s\) extracted from peak inhale phase and \(HU_{exh}(s + u_{exh})\) stands for mean intensity of the same supervoxel \(s\) mapped to peak exhale breathing phase by deformation \(u_{exh}\).

Then all voxels belonging to the particular supervoxels are assigned the estimated ventilation value from Eq. 7.

In the approach of [24, 58] (referenced to, henceforth, as ‘classic approach’), described in Sec. 1, images are preprocessed using Gaussian filtering to compensate for mis-registration or other image artefacts. Therefore the ventilation of each voxel is influenced by all of its neighbors within a certain spatial distance. We propose to estimate the ventilation for groups of voxels
which are both spatially close and have similar intensity values. Such a formulation should more accurately correspond to anatomical structure of the lungs.

A particular clustering can have a strong influence on the results of the estimated ventilation maps. As we do not put additional explicit constrains on the shape and size of the supervoxels, they might result in mis-segmentations. To address this issue, we propose to perform the extraction of a number of layers of supervoxels, akin to [18], where a similar approach has been applied to deformable image registration. Such an approach has been shown to improve the robustness of the method, as well as reduce the influence of the particular clustering and the need to add further constrains to the clustering. Therefore we perform supervoxels clustering several times, each time changing slightly the initial clustering parameters, which results in different clusterings. Then the final estimated ventilation for a voxel is calculated as the average over all the layers of supervoxels:

$$\overline{\text{Vent}_{SLIC}} = \frac{1}{n} \sum_{i=1}^{n} \text{Vent}_{SLIC}^n,$$

where $n$ is the number of layers of supervoxels. A visualization of the ventilation maps from both methods and XeMRI for Patient 2 is shown in Fig. 2. To further improve the results, we apply Gaussian filtering with a small [7 7 7] kernel and $\sigma = 1$ voxel over the final $\overline{\text{Vent}_{SLIC}}$.

2.3. XeMRI to CT alignment

In order to perform the evaluation of the correlation between 4DCT-based estimated ventilation maps and XeMRI ventilation images, we need to
bring these volumes into alignment. XeMRI ventilation images lack structural information. Therefore, their direct registration with CT would be an extremely challenging task. To address this issue we decided to first correct for the misalignment between XeMRI and pMRI with an affine registration method. Then we performed pMRI to CT registration. This task is thus divided into two steps: affine registration with mutual information as a similarity measure, which is followed by deformable registration with the use of deeds method [44].

3. Experiments and Results

We have conducted a number of experiments in which we have investigated different aspects of the estimated ventilation maps. We start from presenting in Sec. 3.1 materials on which we perform our experiments. In the following Sec. 3.2 and Sec. 3.3 we investigate the influence of the supervoxels size and the number of layers of supervoxels, respectively. Then, in Sec. 3.4 we calculate correlation coefficients between estimated ventilation maps and XeMRI. In Sec. 3.5 we evaluate the spatial overlap based on ventilation percentile ranges.

3.1. Materials

We performed the evaluation of the proposed method based on three cases (two male, one female, with ages ranging from 62 to 71 years old) consisting of 4DCT and XeMRI/pMRI data for patients undergoing radiotherapy treatment at Churchill Hospital in Oxford. The patients suffered from lung cancer stage II. The cancer staging for the patients was T2a-T3/4, N1-N2, and M0. 4DCT was acquired on a GE Optima CT580 RT scanner with phase sorting.
The patients lied supine on the couch with arms held above their head, and were coached on how to maintain regular tidal breathing. A mixture of $^{129}$Xe gas (80%) and air was polarized on-site to between 4% and 12%, by using a commercial polarizer (Model 1651; GE Healthcare, Milwaukee, Wisconsin, USA) operating on the rubidium vapor spin-exchange optical pumping basis, and deposited in a Tedlar bag (Jensen Inert Products, Coral Springs, Florida, USA). Hyperpolarized $^{129}$Xe was administered by first instructing the subjects, who were lying supine in the MR imaging unit, to exhale to Functional Residual Capacity (FRC) and then inhale the 1.0 liter contents of the Tedlar bag through 9.5mm inner diameter Tygon tubing (Cole-Palmer Instrument; Hanwell, London, UK). Subjects were then instructed to hold their breath for up to 25 seconds for image acquisition [65]. The pMRI and XeMRI scans were obtained with a 1.5-T whole-body system (Signa HDx; GE Healthcare). The spatial resolution of the XeMRI/pMRI is 1.56x1.56x20 mm$^3$, whereas for CT it is 0.977x0.977x2.5 mm$^3$. All data were resampled to an isotropic resolution of 1x1x1 mm$^3$ size. The sequence of 4DCT consisted of 10 volumes of different breathing phases. Due to the rarity of the data and the limited number of available datasets, we could not create separate training and testing datasets. In the presented study, we chose one random dataset to pre-tune the parameters of the proposed method and then fixed them for the other two. This process was repeated three times, for each of the cases. In such a way we found Gaussian kernel parameters and initial settings for the size of the supervoxels. During this procedure we used only one image registration method: deeds, fixed for all the cases.
3.2. Influence of the supervoxel size

The size of the supervoxels is one of the factors that have an influence on the results of the estimated ventilation maps. On the one hand, supervoxels that are too large may not be capable of modeling the regional nature of the ventilation changes. On the other hand, if too small, the supervoxels might lose their structure-oriented properties and provide similar results to the voxel-wise approaches. The purpose of this experiment is to investigate how the size of the supervoxels influences the correlation of the estimated ventilation maps with XeMRI ventilation images, and if there is a local maximum indicating an optimal size of the supervoxels. To investigate these properties, we have measured the correlation of the SLIC-based
estimated ventilation maps with XeMRI using different supervoxel sizes. We have extracted approximately 1,000, 2,000, 5,000 and 10,000 of supervoxels from each volume. The experiments were conducted with a fixed number of supervoxel layers, namely 15, which is a reasonable trade-off between performance and computational requirements. We have performed the same experiment for all of the registration methods. In Fig. 3 we present a plot showing the trend for average results on a logarithmic scale. The detailed results for each individual case are presented in Appendix A.

For a sparse image representation with a low number of large supervoxels, the results show relatively poor correlation with XeMRI. However, by increasing the number of supervoxels, and hence, reducing their size, we find that the correlation reaches its maximum for approximately 2,000 supervoxels extracted from a volume. Results gradually decay for increasing number of supervoxels of decreasing size. All image registration methods exhibit a similar trend in their correlation with XeMRI.

3.3. *Influence of the number of layers*

The number of layers of supervoxels has an obvious influence on the estimated ventilation images. Using just a single layer of supervoxels, the results might be biased by the particular image clustering. By applying a larger number of layers, the results should be more robust and we would expect the correlation with XeMRI to be higher. We conducted an experiment investigating the influence of the number of layers of supervoxels on the correlation between the estimated ventilation maps with XeMRI for all four image registration methods. We estimated ventilation maps for 1, 5, 10, 15 and 25 layers of supervoxels. The size of the supervoxels was adjusted based on the previ-
Figure 4: The plot shows the influence of the number of supervoxel layers on the correlation of the estimated ventilation maps with XeMRI ventilation images for all four registration methods. The correlation improves when the number of layers is increased, reaching a plateau for 25 layers.

Dense experiments to approximately 2k supervoxels per volume. The obtained average results are shown in Fig. 4. The detailed results for each individual case are presented in Appendix B. The proposed method achieves relatively low correlation when there is just one layer of supervoxels. The results improve noticeably after increasing the number of layers to 5 layers, while there is a more gradual improvement up to 15. With the use of more than 15 layers of supervoxels the correlation between XeMRI and the investigated ventilation surrogates estimated using different image registration methods reaches a plateau, with only slight improvement for 25 layers. Similar trends can be observed independently of the applied registration method.
We investigate the results for all four image registration methods: deeds, demons, demons with BLF and supervoxel graph cuts. For each of them we calculate all four estimates of the ventilation. We present average results for all three patients from our dataset. The highest Dice overlap was achieved for the proposed method in red. It can be noticed that similar patterns in the results can be observed for all of the tested image registration methods.

3.4. Global correlation

To investigate the global relation of the estimated ventilation maps with XeMRI we calculate Spearman’s correlation coefficient for all methods: the classic intensity based [24, 38], the proposed SLIC-based, Jacobian based [36, 37] and HU averaging [39]. Despite the fact that the classic intensity based, Jacobian based and HU averaging methods were not initially developed for the evaluation on hyperpolarized gas MRI, they have been successfully used to study and compare ventilation surrogates with this ventilation
Table 1: Spearman’s correlation coefficients calculated for all ventilation estimation methods. For the classic methods, SLIC-based and Jacobian-based we present results achieved by investigated image registration methods. In the case of HU-Avg no image registration method was applied. The highest correlations have been achieved for the proposed SLIC-based method.

<table>
<thead>
<tr>
<th>Pat. no.</th>
<th>Classic</th>
<th>SLIC</th>
<th>Jacobian</th>
<th>HU-Avg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>demons</td>
<td>demons</td>
<td>graph</td>
<td>demons</td>
</tr>
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<td>0.356</td>
<td>0.348</td>
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<td>0.605</td>
<td>0.598</td>
<td>0.645</td>
<td>0.633</td>
</tr>
<tr>
<td>3</td>
<td>0.279</td>
<td>0.256</td>
<td>0.186</td>
<td>0.198</td>
</tr>
<tr>
<td>Avg</td>
<td>0.363</td>
<td>0.386</td>
<td>0.396</td>
<td>0.393</td>
</tr>
</tbody>
</table>

imaging method [26, 28]. For all these methods we have used \( G_{k1} = G_{k2} \) with [15 15 15] voxel kernels size and \( \sigma = 2 \) voxels, as these settings have been previously reported in the literature [28, 39], and were shown to reach plateau in terms of correlation with hyperpolarized gas MRI ventilation [28]. Only from the proposed SLIC-based method we applied a smaller, [7 7 7] voxel kernel size filter with \( \sigma = 1 \) voxel. We refer an interested reader on the influence of the applied filter sizes on the correlation of the ventilation surrogates with hyperpolarized gas MRI to, for instance, [28]. The image registration methods used to estimate the deformations for ventilation surrogates were applied with the parameters optimized by their authors when evaluated on Dir-Lab dataset [52].

In this experiment, we achieved a higher correlation for our method compared with the others, when applied voxel-wise manner on average for all cases. The best results were obtained independently of the chosen image registration method. The classic approach achieved higher correlation compared with HU averaging method for all image registration methods, apart from the classic demons method. The lowest correlations with XeMRI were
obtained for the Jacobian-based method for all registration methods. Only for this ventilation estimation approach, demons BLF achieved higher correlation than supervoxel graph cuts for one of the cases, yet still lower than the deeds method. The numerical results are presented in Table 1. Visualization of the estimated ventilation maps for one of the cases is shown in Fig. 2.

The visualization of the results is presented in Fig. 6 for all cases. We also calculate correlation between the proposed ventilation estimation method and the classic, showing that they correlate well (0.834), with the proposed method achieving the best correlation with XeMRI.

Worth noticing is relatively high correlation achieved by the HU-Avg method. The method has failed to provide local estimates of the ventilations, resulting in a blurred image of the shape of the lungs. Such an explanation can be confirmed by a closer investigation of the visual results in Fig. 2 where the ventilation surrogates for one of the patients are presented. Similar behavior was observed throughout the dataset. In our experiments we could hardly observe local patterns of the ventilation changes. We also could not see the trend visible for other methods where the results of the correlation with XeMRI for patient 2 were noticeably higher than for the other two.

For Jacobian-based ventilation the results obtained by different image registration methods are more consistent than for the classic and SLIC-based, especially for patient 1 and 3.

3.5. Spatial overlap comparison

We have performed a series of experiments investigating the quantitative relation between the spatial distribution of the estimated ventilation maps and XeMRI ventilation images. Akin to [59], we have divided the estimated
Figure 6: The figure shows correlation and Spearman correlation coefficient between the HU averaging ventilation approach and XeMRI in the first column. In the second column, correlation and Spearman correlation coefficient between the Jacobian-based ventilation approach and XeMRI are presented. In the following columns analogical correlations are presented for the classic approach and for the proposed SLIC-based method. In the last column, correlation between the classic and the proposed method are shown. Rows correspond to patient’s number.
ventilation images into five disjoint regions, based on calculated percentile distribution ranges. These regions were further used to create masks corresponding to the percentile ranges. For each of them, we calculated the Dice overlap coefficient with corresponding masks of XeMRI. We have applied this procedure to all four lung ventilation estimation methods and repeated the experiments for all investigated image registration approaches.

The visualization of the results is presented in Fig. 5. The general trend, where Dice overlap is the highest for the first percentile range (0-20%), for the intermediate ranges is lower, and then raises for the last percentile range (81-100%) is in agreement with similar experiments in the literature [59]. Similar patterns in the results can be observed for all of the tested image registration methods. For all of the evaluated percentile ranges, the highest correlation has been achieved for our proposed method (in red). The lowest Dice overlap has been obtained for the Jacobian-based ventilation method. The classic approach and HU averaging method achieved similar results. The results for the HU averaging method are independent of the image registration methods. However, we decided to include them in the plots showing the results of the correlation for different image registration methods to enable the comparison with them.

4. Discussion and Conclusions

In this work, we have introduced and investigated the patch-based approach for ventilation estimation. We have conducted a number of experiments, measuring the correlation of the estimated ventilation maps with XeMRI ventilation images. To perform this evaluation, we have proposed
a registration framework to bring SLIC-based ventilation images into alignment with XeMRI. The presented results show that the proposed method results in higher correlation with XeMRI for a number of performed tests.

We have investigated the influence of the supervoxel size in Sec. 3.2 for all of the image registration methods. In the results presented in Fig. 3 we can observe that to achieve the best correlation the size of the supervoxel needs to be chosen with care. In our experiments we have found out that the highest correlation has been achieved for approximately 2,000 supervoxels per volume. This means that the average supervoxel consists of 30,000 isotropic 1x1x1mm$^3$ voxels. This is related to their ability to model the anatomy of the lungs. This trend in the changes of correlation has been expected and supports our claim that structure-oriented patch-based approach is a better choice than a voxel-wise approach. The limited number of available cases did not allow us to create separate training and testing datasets. Apart from the image registration methods settings, all other parameters of the presented ventilation estimation method were trained and tested with the use of the available dataset in a manner described in Materials section. The chosen approach might be seen as suboptimal, however due to the unique character of the dataset, creation of the separate training and testing datasets based on them was not feasible. Further evaluation on the larger dataset would be required to draw meaningful conclusions about superiority of the proposed method compared to other approaches.

The results from Sec. 3.3 show that a larger number of layers of supervoxels provides images more correlated with XeMRI. This is expected, as a larger number of layers of supervoxels should improve the robustness of
the method for mis-segmentations originating from a particular supervoxel extraction. In our work we have not investigated the influence of the compactness of supervoxels because the intention is for the supervoxels to mimic the anatomy of the lungs. Therefore, this parameter was adjusted manually to make the supervoxels correspond in shape to lung structures.

When investigating the influence of the number of supervoxels on the correlation between XeMRI and ventilation surrogates, we have applied a number of different image registration methods. Despite differences in approaches of the studied methods, we have observed a similar trend of the correlation for all of them. This observation suggests that the proposed method is not restricted to one of the evaluated methods, but is more universal, as the methods investigated in our study represent the main registration categories in terms of optimization, namely: discrete, continuous, and hybrid. Given the small number of cases analysed, we cannot provide a definitive answer as to whether the registration methods are equivalent; however, we believe the similarity of the results provides some reassurance as to the robustness of the method in this respect.

The results presented in Sec. 3.4, where the classic demons image registration method was compared with its sliding motion preserving version, show that the incorporation of the sliding motion improves the correlation of the estimated ventilation maps with XeMRI. This observation supports the claim that sliding motion preservation results in more anatomically plausible deformations of the registration. The deeds [44] and supervoxel graph cuts [46] methods showed slightly more accurate performance on the Dir-Lab dataset [52] than both demons methods, which is also reflected in the higher
correlations calculated for these methods. The difference between the correlations calculated for the deeds [44] and supervoxel graph cuts [46] for all ventilation estimation methods is minimal (below 0.01). This might suggest that even though both methods represent different approaches to the image registration problem, both cope well with the task providing similar level of accuracy. This also suggests that more accurate image registration methods provide estimations of ventilation which result in higher levels of correlation with XeMRI.

The analysis of the Dice overlap for the ventilation percentile ranges shows favorable performance of our method for all investigated ranges. The Jacobian-based ventilation maps resulted in lower correlation with XeMRI than the classic approach. This observation is in agreement with previous findings from [58]. An interesting observation is that the HU averaging methods achieves comparable results to the classic approach. Especially in the context of the results reported in [39], where the authors found low correlation for the patients with severe ventilation defects, which is also the case in our study.

In our work we have investigated the influence on the correlation of the estimated ventilation with XeMRI of using four different image registration methods. They represent distinct approaches to the task, covering most of the existing groups of methods. We did not aim to evaluate which of the registration methods performed best, but rather wanted to show the general trend that the application of our supervoxel-based ventilation estimation improves the correlation to XeMRI ventilation maps, irrespective of the underlying image registration.
An open point for a discussion might be whether the achieved level of correlation reaches the expectations and is applicable to enhance radiotherapy. The proposed SLIC-based method and the classic approach were able to identify severe ventilation defects, as shows an example in Fig. 2. Precise localization of the ventilation defects remains challenging to evaluate. In a recent study [66], the researchers have evaluated and compared ventilation maps estimated on 4DCT and high quality exhale/inhale breath-hold CT (BHCT) with Galligas PET. They found that ventilation maps estimated using BHCT achieved higher correlation values. Such an observation may be mainly due to reconstruction artifacts present in 4DCT, and could suggest that the application of BHCT has the potential to improve the accuracy of the estimated ventilation maps. Additionally, in our opinion an improved pMRI to CT registration, which brings XeMRI to the alignment with CT, plays an important role in this evaluation. The method applied in our study, as well as methods applied by other researchers were not developed strictly for this task. Therefore, the pattern of the regularization applied inside of the lungs might not be fully corresponding with the anatomy of the lungs.

A detailed analysis including a larger group of patients could further support our results. The presented results, where for the majority of the conducted experiments the proposed method for ventilation estimation from 4DCT achieves better correlations with XeMRI images, indicate higher physiological consistency of our proposed approach using supervoxels for ventilation estimation. In future, we are planning to perform further analysis on a larger patient group. Another crucial issue is XeMRI to CT registration.

We could observe the improvement in the correlation for more accurate im-
age registration methods. We would expect further improvements when task
dedicated registration between pMRI and CT was applied. Due to a lim-
ited amount of information on inner lung structure in pMRI, the standard
image registration methods might be suboptimal for this task and dedicated
frameworks could potentially provide more accurate results [67].

We have presented a proof of concept for a patch-based ventilation estima-
tion method from 4DCT. We have shown that our proposed method achieves
higher correlation coefficients compared to the classic approach when corre-
lated with XeMRI. The results, already encouraging at the current stage,
would gain on significance when evaluated on a larger cohort of patients,
where separate training and testing datasets would be applied.

Conflict of interest

The authors have no conflict of interest to disclose.

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NIHR Biomedical Research Centre (Rutherford Fund Fellowship at HDR
UK). We would also like to acknowledge M. Heinrich for making his code for
the deeds image registration method [44] available online.
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Appendix A Influence of the supervoxel size

Here, we present detailed numerical results calculated for the influence of the supervoxel size, based on which plots from Fig. 3 were prepared. The provided Tables 2, 3, 4, 5 were used to create Fig. 3, where we investigate the influence of the supervoxel size on the Spearman correlation between the results of the proposed estimated ventilation method and XeMRI ventilation images. In Tables 2, 3, 4, 5 we have shown the results calculated for the different image registration methods, the deeds [44], demons [45], BLF [41] and supervoxel graph cuts [46], respectively.

Table 2: The influence of the size of supervoxels on the Spearman correlation between 4DCT-based estimated ventilation maps using the deeds [44] registration method and XeMRI ventilation images.

<table>
<thead>
<tr>
<th>Patient</th>
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<th>~ 2k</th>
<th>~ 5k</th>
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<tr>
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<td>0.421</td>
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<td>0.209</td>
<td>0.282</td>
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<tr>
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<td>0.479</td>
<td>0.454</td>
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</table>
Table 3: The influence of the size of supervoxels on the Spearman correlation between 4DCT-based estimated ventilation maps using the demons [45] registration method and XeMRI ventilation images.

<table>
<thead>
<tr>
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<td>0.660</td>
<td>0.651</td>
</tr>
<tr>
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<td>0.336</td>
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<td>Avg</td>
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<td>0.449</td>
<td>0.437</td>
<td>0.415</td>
</tr>
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</table>

Table 4: The influence of the size of supervoxels on the Spearman correlation between 4DCT-based estimated ventilation maps using BLF demons [41] registration method with sliding motion preservation and XeMRI ventilation images.

<table>
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<tr>
<th>Patient</th>
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<td>0.641</td>
</tr>
<tr>
<td>3</td>
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<td>0.435</td>
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Table 5: The influence of the size of supervoxels on the Spearman correlation between 4DCT-based estimated ventilation maps using supervoxel-based graph cuts [46] registration method with sliding motion preservation and XeMRI ventilation images.

<table>
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<tr>
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<tr>
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<td>0.278</td>
<td>0.264</td>
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<tr>
<td>Avg</td>
<td>0.400</td>
<td>0.474</td>
<td>0.458</td>
<td>0.447</td>
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</tbody>
</table>

Appendix B Influence of the number of supervoxel layers

We present here detailed numerical results calculated for the influence of the number of supervoxel layers on Spearman correlation between estimated ventilation surrogates and XeMRI, based on which plots from Fig. 4 were prepared.

Table 6: The influence of the number of layers of supervoxels on the Spearman correlation of XeMRI with deeds [44] registration method based ventilation surrogates.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1 layer</th>
<th>5 layers</th>
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</thead>
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<tr>
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<td>0.280</td>
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</tr>
<tr>
<td>Avg</td>
<td>0.425</td>
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<td>0.484</td>
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</table>
Table 7: The influence of the number of layers of supervoxels on the Spearman correlation of XeMRI with demons [45] registration method without sliding motion preservation based ventilation surrogates.

<table>
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<tr>
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<tr>
<td>3</td>
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<tr>
<td>Avg</td>
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Table 8: The influence of the number of layers of supervoxels on the Spearman correlation of XeMRI with BLF demons [41] registration method with sliding motion preservation based ventilation surrogates.

<table>
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Table 9: The influence of the number of layers of supervoxels on the Spearman correlation of XeMRI with supervoxel-based graph cuts [46] registration method based ventilation surrogates.

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<td>Avg</td>
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</table>
Patch-based Lung Ventilation Estimation using Multi-layer Supervoxels

Highlights:

- A novel method for lung ventilation estimation using supervoxels and deformable image registration.
- The method tracks changes of the intensity in the supervoxels extracted from peak exhal breath phase of 4D Computed Tomography (CT).
- A correlation between the estimated ventilation maps with ventilation images acquired from hyperpolarized Xenon129 MRI is calculated.
- The results suggest that the presented technique may be advantageous for CT-based ventilation estimation, when compared with other methods for estimating ventilation.
- Our method is shown to perform favorably to other ventilation estimation methods commonly used in the field, independently of the image registration method applied to 4DCT.