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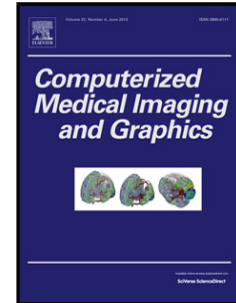
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Author: Adam Szmul Tahreema Matin Fergus V. Gleeson
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Patch-based Lung Ventilation Estimation using Multi-layer Supervoxels

Adam Szmul^a, Tahreema Matin^b, Fergus V. Gleeson^{b,c}, Julia A. Schnabel^{a,d}, Vicente Grau^a, Bartłomiej W. Papież^{a,e}

^a*Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, UK,*

^b*Department of Oncology, University of Oxford, UK*

^c*Department of Radiology, Oxford University Hospitals NHS FT, Oxford, UK*

^d*Department of Biomedical Engineering, School of Biomedical Engineering and Imaging Sciences, King's College London, UK*

^e*Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, UK*

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

Email address: adam.szmul@eng.ox.ac.uk (Adam Szmul)

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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

2 Patch-based methods have become an essential tool in many fields of
3 computer vision and medical imaging. In computer vision they are used for

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

13 A potential application of patch-based methods is to estimate regional
14 ventilation of the lungs based on 4DCT. This is an important application, as
15 pulmonary-related diseases are among the leading causes of death worldwide
16 [20]. Lung cancer is the most common cause of cancer death and the second
17 most commonly diagnosed cancer type in both male and female populations
18 [21], and Chronic Obstructive Pulmonary Disease (COPD) is responsible for
19 nearly twice as many deaths as breast cancer [20]. Tests measuring overall
20 lung condition may not be specific enough to help localize and confront these
21 challenging diseases [22]. The gold standard test for pulmonary function is
22 the spirometry technique, which evaluates global lung function by measuring
23 the volume and speed of air during inhalation and exhalation. Although
24 this method is cheap, fast, and widely used as a screening tool [23], it lacks
25 regional lung evaluation and thus cannot be used for precision medicine such
26 as individualized radiotherapy planning [24]. Assessment of the regional
27 lung functionality has the potential to provide more accurate radiotherapy
28 treatment [25], which could spare well-functioning parts of the lungs and be

29 used for follow up to evaluate the treatment effectiveness.

30 The estimation of ventilation surrogates based on CT images is an active
31 field of research. In [26], for instance the Dice overlap of percentage ven-
32 tilation volumes between 4DCT originating ventilation estimates and ^3He
33 MRI was investigated, and no significant difference was found. That study
34 supports the claim that well-ventilated regions in 4DCT-based ventilation
35 surrogates and ^3He MRI are in agreement. A lobar oriented analysis of lung
36 ventilation was presented in [27], where the authors compared CT-based ven-
37 tilation surrogates with ^3He MRI for asthma patients. The authors found
38 agreement between the investigated ventilation imaging methods. An inter-
39 esting study was presented in [28], where, apart from investigating the corre-
40 lation between different CT-based ventilation estimation techniques and hy-
41 perpolarized gas MRI ventilation images, the correlation between ^3He MRI
42 and ^{129}Xe MRI was evaluated. They found significantly lower correlation
43 between CT originating ventilation surrogates and hyperpolarized gas MRI
44 ventilation maps than between ^3He MRI and ^{129}Xe MRI. In order to search
45 for the best indicator of lung function, the authors of [29] investigated corre-
46 lation between ventilation estimated from ^{129}Xe MRI and the quantity of gas
47 transferred to red blood cells (RBCs). Their initial conclusion was that ^{129}Xe
48 MRI ventilation may not be the optimal measure of the true regional lung
49 function. Despite the amount of work done in the field, there is still scope
50 for further research in the methods dedicated for estimating ventilation from
51 CT images.

52 *1.1. Aims*

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

- 59 1. We present, in detail, the proposed method for regional ventilation es-
60 timation, including a thorough investigation of the influence of relevant
61 parameters.
- 62 2. We show the performance of our approach for different image registra-
63 tion methods.
- 64 3. We provide a quantitative comparison between state-of-the-art meth-
65 ods for lung ventilation estimation and the proposed method.
- 66 4. We correlate our results with XeMRI using the developed registration
67 approach between proton density MRI (pMRI) and CT, which we ex-
68 plain in detail.

69 The remaining part of this section is organized as follows: in Sec. 1.2
70 we present lung ventilation imaging methods based on MRI and CT. Subse-
71 quently, in Sec. 1.3 we discuss lung image registration when applied to lung
72 CT. We follow this by introducing lung ventilation estimation techniques
73 based on 4DCT in Sec. 1.4.

74 *1.2. Lung Ventilation Imaging*

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

95 4DCT, on the other hand, is a structural imaging technique routinely used
96 for radiotherapy planning, where images are acquired during free breathing
97 under spirometry control. It can be used to estimate lung ventilation maps,
98 based on the results of the registration between peak-exhale and peak-inhale

99 breathing phase volumes. 4DCT based ventilation methods can be roughly
100 classified into those, which rely on the value of the determinant of the Jaco-
101 bian matrix of the deformations to estimate the lung volume change [36, 37],
102 methods tracking the changes in the intensity of the lungs quantified in
103 Hounsfield units (HU) [38, 24], and those based on averaging a product of
104 air and tissue fraction across all breathing phases [39]. Changes in tissue
105 attenuation correspond to variations in tissue density and originate from fill-
106 ing the lungs with air. The Jacobian-based and intensity tracking methods
107 require estimation of the deformation field between peak breathing phases
108 from 4DCT, performed by deformable image registration. In contrast, the
109 averaging method [39] does not need to estimate deformations.

110 1.3. Lung Image Registration

111 The task of deformable image registration is to bring two or more images
112 into alignment, based on a specified similarity measure. To ensure not only
113 a perfect match for each voxel but also plausibility of the estimated defor-
114 mation field, a regularization is required. This can be done, for instance, by
115 incorporating it into a transformation model, such as Free Form Deforma-
116 tions (FFDs) with B-Splines [40], by adding an additional regularization term
117 to the optimization [41, 42], or by incorporating sparse key-points matching
118 [43].

119 To investigate the robustness of the proposed ventilation estimation method
120 on the applied image registration method, we used a number of different ap-
121 proaches: the deeds method [44], classic demons method [45], its extended
122 version applying bilateral filtering (BLF) [41], and supervoxel-based graph
123 cuts [46]. The aim of this experiment is to evaluate if the obtained patterns

124 in the results are independent of the applied image registration method to
125 estimate deformations, rather than to determine which of the methods is the
126 most suitable for this application.

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

134 The second investigated method is the well established demons method
135 [45, 47]. In the primary work [45], the optimization is performed in an
136 alternate way, in which finding the best displacement at each iteration for
137 every voxel is followed by a filtering of the estimated displacement field, where
138 the filtering works as a regularization. The method was later extended to
139 preserve diffeomorphism [47]. The authors used Gaussian filtering, which
140 did not take into account the discontinuities appearing at the borders of
141 the lungs. Such a limitation was shown to result in the underestimation of
142 displacements near the borders of the lungs. We will refer to this method as
143 demons.

144 The third evaluated method is an extension of the previous. In [41], the
145 authors addressed the problem of preservation of discontinuities at the bor-
146 ders of the lungs, called sliding motion, by introducing an additional filtering
147 kernel in the form of bilateral filtering (BLF) [48]. The method showed an
148 improvement in accuracy of the results, as well as more anatomically plau-

149 sible deformations, especially within problematic lung regions. We will refer
150 to this method as demons BLF.

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

164 All of the methods have shown good performance in a publicly available
165 Dir-Lab dataset [52], with 300 manually annotated landmarks provided for
166 evaluation purpose. The deeds method resulted in Target Registration Er-
167 ror (TRE) on the dataset of 1.43mm, for Demons and their BLF extension
168 TREs of 2.35mm and 1.95mm were measured, respectively, and for the su-
169 pervoxel graph cuts TRE was 1.16mm. All registration methods used for
170 the evaluation of our new method for ventilation estimation were optimized
171 using Dir-Lab, and all of them were optimized by their authors to get the
172 best TRE on Dir-Lab. We have applied them with the provided parameters.
173 These image registration method parameters were set completely indepen-

174 dent of our testing dataset. There are other lung image registration methods
 175 [53, 54] and even approaches dedicated for lung mass/tissue preserving dur-
 176 ing the alignment process [55, 56, 57]. These methods, though presenting an
 177 interesting approach for enhancing similarity measure, resulted in moderate
 178 performance when evaluated on the Dir-Lab dataset. Our choice covers main
 179 registration categories in terms of optimization, namely: discrete, continuous,
 180 and hybrid.

181 1.4. Ventilation Estimation from 4DCT

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

188 *Intensity/Density Change Ventilation Estimation Method:* One of the ap-
 189 proaches for ventilation estimation from 4DCT is to track changes in lung
 190 intensity throughout the breathing process. As CT intensity is directly re-
 191 lated to the tissue density, it reflects the changes originating from filling the
 192 lungs with air. Following [24, 58], the ventilation is estimated for the full
 193 exhale phase:

$$Vent_{Dens}^{exh}(\mathbf{x}) = \left(\frac{HU_{exh}(\mathbf{x}) * G_{k1} - HU_{inh}(\mathbf{x} + \mathbf{u}_{inh}) * G_{k1}}{HU_{inh}(\mathbf{x} + \mathbf{u}_{inh}) * G_{k1} + 1000} \right) * G_{k2}, \quad (1)$$

194 with $HU_{exh}(\mathbf{x} + \mathbf{u}_{exh})$ being an intensity value expressed in Hounsfield units
 195 (HU) for a voxel at spatial position \mathbf{x} of the peak exhale phase image warped

196 towards the peak inhale phase image by the displacement field \mathbf{u}_{inh} . Similarly,
 197 $HU_{inh}(\mathbf{x})$ represents intensity value of peak inhale image for the same voxel \mathbf{x} .
 198 G_{k1}, G_{k2} are Gaussian kernels used for smoothing and convolved (denoted by
 199 $*$ in the equation) with the images. Some researchers substituted Gaussian
 200 kernels with box filter kernels, [59], or with median filter kernels, [28, 60]. In
 201 our study we followed the original formulations of [24, 58], therefore, we will
 202 subsequently refer to the Gaussian filtering. The investigation of the influence
 203 of the applied filtering methods was out of the scope of this work. In [61]
 204 the authors investigated the reproducibility of the intensity-based approach
 205 for a number of different parameters and cases. All the image intensities are
 206 given in HU.

207 *Jacobian-based Method:* Local lung volume change can be used as a mea-
 208 sure of lung ventilation [36]. The determinant of the Jacobian of deformations
 209 estimated by deformable registration between different breathing phases is.

$$Vent_{JAC}(\mathbf{x}) = \begin{vmatrix} 1 + \frac{\partial u_x(\mathbf{x})}{\partial x} & \frac{\partial u_x(\mathbf{x})}{\partial y} & \frac{\partial u_x(\mathbf{x})}{\partial z} \\ \frac{\partial u_y(\mathbf{x})}{\partial x} & 1 + \frac{\partial u_y(\mathbf{x})}{\partial y} & \frac{\partial u_y(\mathbf{x})}{\partial z} \\ \frac{\partial u_z(\mathbf{x})}{\partial x} & \frac{\partial u_z(\mathbf{x})}{\partial y} & 1 + \frac{\partial u_z(\mathbf{x})}{\partial z} \end{vmatrix} \quad (2)$$

210 with u_x, u_y, u_z being the deformation fields estimated in x, y and z directions
 211 respectively. The determinant of the Jacobian of the deformations taking val-
 212 ues between 0 and 1 indicate for shrinking the lung volume, values of 1 mean
 213 no volume change for the region and values over 1 indicate volume expansion
 214 calculated for a spatial location \mathbf{x} . Such an approach has been applied in [37],
 215 where XeCT-based ventilation volumes were compared with the ventilation
 216 estimated based on the determinant of the Jacobian. Recently a sensitiv-
 217 ity analysis of the determinant of the Jacobian for lung cancer treatment

218 planning has been presented [62]. The reproducibility of the Jacobian-based
 219 ventilation has been investigated in [63]. It has been shown that the method
 220 correlates well with lung function in emphysema patients [58].

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

$$Vent_{HU}(\mathbf{x}) = \frac{1}{N} \sum_{\phi=1}^N V_{\phi}(\mathbf{x}) \quad (3)$$

$$V_{\phi}(\mathbf{x}) = \begin{cases} \frac{HU_{\phi}(\mathbf{x})}{-1000} \times \frac{HU_{\phi}(\mathbf{x})+1000}{1000} & \text{for } \mathbf{x} \in L(\phi) \\ 0 & \text{for } \mathbf{x} \notin L(\phi) \end{cases} \quad (4)$$

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

238 The remaining part of this paper is organized in the following way: in

239 Sec. 2 we introduce our proposed method for estimating ventilation in a
240 patch-based manner. The results of the proposed experiments are presented
241 in Sec. 3, which are finally discussed and concluded in Sec. 4.

242 **2. Methods**

243 In this section we present the proposed supervoxel-based lung ventilation
244 estimation method. We introduce the image clustering method in Sec. 2.1,
245 as well as explain how we apply it to the proposed method in Sec. 2.2. A
246 work-flow diagram presenting the method is shown in Fig. 1. Finally in Sec.
247 2.3 we present the proposed image registration framework in which we bring
248 the estimated ventilation maps from 4DCT to align with XeMRI ventilation
249 images.

250 *2.1. Supervoxel clustering*

251 One of the approaches for patch-based methods is supervoxel-based im-
252 age representation. Supervoxel-based image clustering groups voxels that are
253 spatially close and visually similar into larger structures. They have become
254 the building blocks for many applications in computer vision and medical im-
255 age analysis. In our formulation, we apply Simple Linear Iterative Clustering
256 (SLIC) [64] as a clustering method, due to its speed of performance and direct
257 control over the number of extracted supervoxels and supervoxel compact-
258 ness. The SLIC method is designed to extract k approximately equally-sized
259 supervoxels. Initially, seeds of the supervoxels are placed on a regular grid at
260 intervals $S = \sqrt[3]{M/k}$ voxels apart, with M being the total number of voxels
261 in the image. In the original work by Achanta [64], the method was proposed
262 for 2D images, whereas here we apply it to 3D supervoxels. The positions of

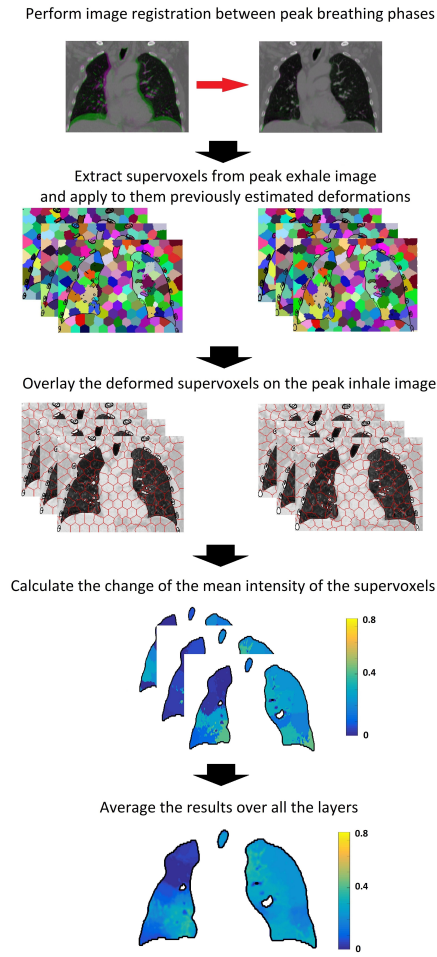


Figure 1: The diagram shows the work-flow of the proposed approach for patch-based lung ventilation estimation. We start by performing deformable image registration between peak breathing phase volumes. We follow that by clustering the peak exhale image into a number of supervoxels. We extract a number 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.

263 the centers are then corrected based on the gradients of the image to prevent
 264 their placement on image edges or at a noisy voxel. Individual voxels are
 265 assigned to the closest cluster based on the distance:

$$\mathcal{Y} = \sqrt{(d_e)^2 + \left(\frac{d_I}{S}\right)^2 m^2}, \quad (5)$$

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

270 2.2. Supervoxel tracking for ventilation estimation

271 The existing methods [24, 36, 39, 58] for estimating ventilation from
 272 4DCT take the structural relationship between voxels into account mainly at
 273 the image registration step or derivatives calculation. In this work we apply
 274 the proposed patch-based method, which additionally addresses structural
 275 relationship directly and estimates ventilation for larger, spatially and visu-
 276 ally consistent regions. Such an approach may be more meaningful from an
 277 anatomical point of view. The lungs are divided into right and left lungs,
 278 which are further separated into lobes, while each lobe consists of a number
 279 of segments. All of them are supplied with separate airways which form a
 280 tree-like structure with no additional interconnections between the subtrees.
 281 Therefore, the ventilation of the neighboring lobes or sections supplied by
 282 different branches of the airway tree may differ. Supervoxels have the poten-
 283 tial to cluster anatomically consistent lung regions and, therefore, ventilation
 284 surrogates would not be estimated across anatomical borders of the lungs.

285 In most of the previous studies ventilation images were estimated for peak
 286 exhale [58]. However in our work we used the peak inhale breathing phase
 287 as a reference, as the difference in the volume of the lungs between pMRI
 288 and CT was then the smallest. Such an approach should result in smaller
 289 deformations applied during pMRI to CT registration and, therefore more
 290 accurate results of the registration. A similar approach has been recently ap-
 291 plied in [28] to address the same challenges. We then formulate an estimate
 292 of the ventilation for peak inhale as follows:

$$Vent_{Dens}^{inh}(\mathbf{x}) = \left(\frac{HU_{exh}(\mathbf{x} + \mathbf{u}_{exh}) * G_{k1} - HU_{inh}(\mathbf{x}) * G_{k1}}{HU_{inh}(\mathbf{x}) * G_{k1} + 1000} \right) * G_{k2} \quad (6)$$

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

298 We start by extracting supervoxels from the peak exhale breathing phase
 299 image and then calculate their mean intensities. Subsequently, we apply the
 300 deformations originating from image registration between peak exhale and
 301 peak inhale breathing volumes to the extracted supervoxels. In this way we
 302 map the same regions, represented by supervoxels, from the peak exhale to
 303 the peak inhale image (see Fig. 1). We recalculate mean intensities of the
 304 transformed supervoxels, this time over the peak inhale image. Then we ap-
 305 ply this approach to the method described above, thus estimating ventilation
 306 for supervoxels rather than for each individual voxel:

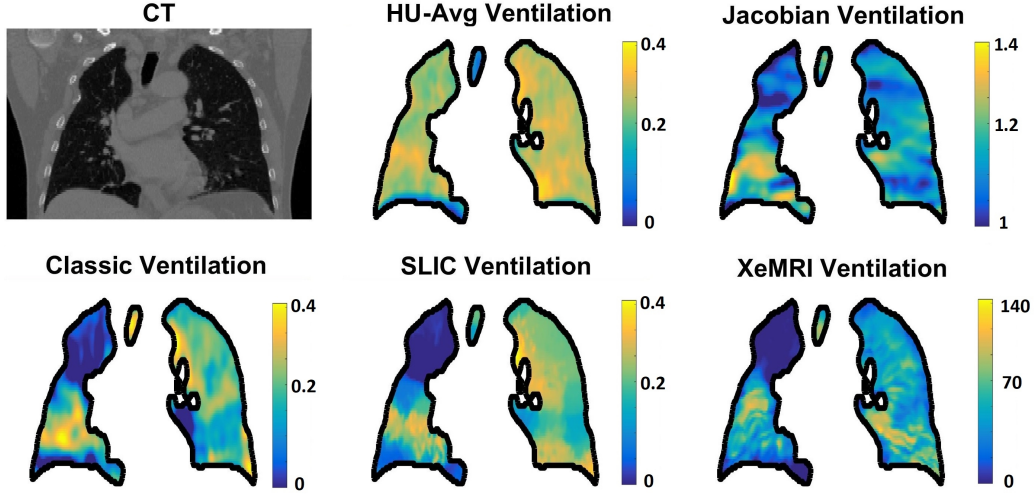


Figure 2: Comparison of the estimated ventilation maps using different methods for Patient 2 in coronal view. The results are presented for the supervoxel graph cuts image registration method. Lung contours extracted from the CT image are propagated onto ventilation images.

$$Vent_{SLIC}(\mathbf{s}) = \frac{\overline{HU_{exh}(\mathbf{s} + \mathbf{u}_{exh})} - \overline{HU_{inh}(\mathbf{s})}}{\overline{HU_{inh}(\mathbf{s})} + 1000}, \quad (7)$$

307 where $\overline{HU_{inh}(\mathbf{s})}$ is the mean intensity of a supervoxel \mathbf{s} extracted from peak
 308 inhale phase and $\overline{HU_{exh}(\mathbf{s} + \mathbf{u}_{exh})}$ stands for mean intensity of the same su-
 309 pervoxel \mathbf{s} mapped to peak exhale breathing phase by deformation \mathbf{u}_{exh} .
 310 Then all voxels belonging to the particular supervoxels are assigned the es-
 311 timated ventilation value from Eq. 7.

312 In the approach of [24, 58] (referenced to, henceforth, as ‘classic ap-
 313 proach’), described in Sec. 1, images are preprocessed using Gaussian filtering
 314 to compensate for mis-registration or other image artefacts. Therefore the
 315 ventilation of each voxel is influenced by all of its neighbors within a certain
 316 spatial distance. We propose to estimate the ventilation for groups of voxels

317 which are both spatially close and have similar intensity values. Such a for-
 318 mulation should more accurately correspond to anatomical structure of the
 319 lungs.

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

$$\overline{Vent}_{SLIC} = \frac{1}{n} \sum_1^n Vent_{SLIC}^n, \quad (8)$$

332 where n is the number of layers of supervoxels. A visualization of the ven-
 333 tilation maps from both methods and XeMRI for Patient 2 is shown in Fig.
 334 2. To further improve the results, we apply Gaussian filtering with a small
 335 $[7 \ 7 \ 7]$ kernel and $\sigma = 1$ voxel over the final \overline{Vent}_{SLIC} .

336 2.3. XeMRI to CT alignment

337 In order to perform the evaluation of the correlation between 4DCT-
 338 based estimated ventilation maps and XeMRI ventilation images, we need to

339 bring these volumes into alignment. XeMRI ventilation images lack struc-
340 tural information. Therefore, their direct registration with CT would be an
341 extremely challenging task. To address this issue we decided to first correct
342 for the misalignment between XeMRI and pMRI with an affine registration
343 method. Then we performed pMRI to CT registration. This task is thus
344 divided into two steps: affine registration with mutual information as a sim-
345 ilarity measure, which is followed by deformable registration with the use of
346 deeds method [44].

347 **3. Experiments and Results**

348 We have conducted a number of experiments in which we have inves-
349 tigated different aspects of the estimated ventilation maps. We start from
350 presenting in Sec. 3.1 materials on which we perform our experiments. In the
351 following Sec. 3.2 and Sec. 3.3 we investigate the influence of the supervox-
352 els size and the number of layers of supervoxels, respectively. Then, in Sec.
353 3.4 we calculate correlation coefficients between estimated ventilation maps
354 and XeMRI. In Sec. 3.5 we evaluate the spatial overlap based on ventilation
355 percentile ranges.

356 *3.1. Materials*

357 We performed the evaluation of the proposed method based on three cases
358 (two male, one female, with ages ranging from 62 to 71 years old) consisting
359 of 4DCT and XeMRI/pMRI data for patients undergoing radiotherapy treat-
360 ment at Churchill Hospital in Oxford. The patients suffered from lung cancer
361 stage II. The cancer staging for the patients was T2a-T3/4, N1-N2, and M0.
362 4DCT was acquired on a GE Optima CT580 RT scanner with phase sorting.

363 The patients lied supine on the couch with arms held above their head, and
364 were coached on how to maintain regular tidal breathing. A mixture of ^{129}Xe
365 gas (80%) and air was polarized on-site to between 4% and 12%, by using
366 a commercial polarizer (Model 1651; GE Healthcare, Milwaukee, Wisconsin,
367 USA) operating on the rubidium vapor spin-exchange optical pumping ba-
368 sis, and deposited in a Tedlar bag (Jensen Inert Products, Coral Springs,
369 Florida, USA). Hyperpolarized ^{129}Xe was administered by first instructing
370 the subjects, who were lying supine in the MR imaging unit, to exhale to
371 Functional Residual Capacity (FRC) and then inhale the 1.0 liter contents
372 of the Tedlar bag through 9.5mm inner diameter Tygon tubing (Cole-Palmer
373 Instrument; Hanwell, London, UK). Subjects were then instructed to hold
374 their breath for up to 25 seconds for image acquisition [65]. The pMRI and
375 XeMRI scans were obtained with a 1.5-T whole-body system (Signa HDx;
376 GE Healthcare). The spatial resolution of the XeMRI/pMRI is $1.56 \times 1.56 \times 20$
377 mm^3 , whereas for CT it is $0.977 \times 0.977 \times 2.5 \text{ mm}^3$. All data were resampled to
378 an isotropic resolution of $1 \times 1 \times 1 \text{ mm}^3$ size. The sequence of 4DCT consisted
379 of 10 volumes of different breathing phases. Due to the rarity of the data
380 and the limited number of available datasets, we could not create separate
381 training and testing datasets. In the presented study, we chose one random
382 dataset to pre-tune the parameters of the proposed method and then fixed
383 them for the other two. This process was repeated three times, for each of
384 the cases. In such a way we found Gaussian kernel parameters and initial
385 settings for the size of the supervoxels. During this procedure we used only
386 one image registration method: deeds, fixed for all the cases.

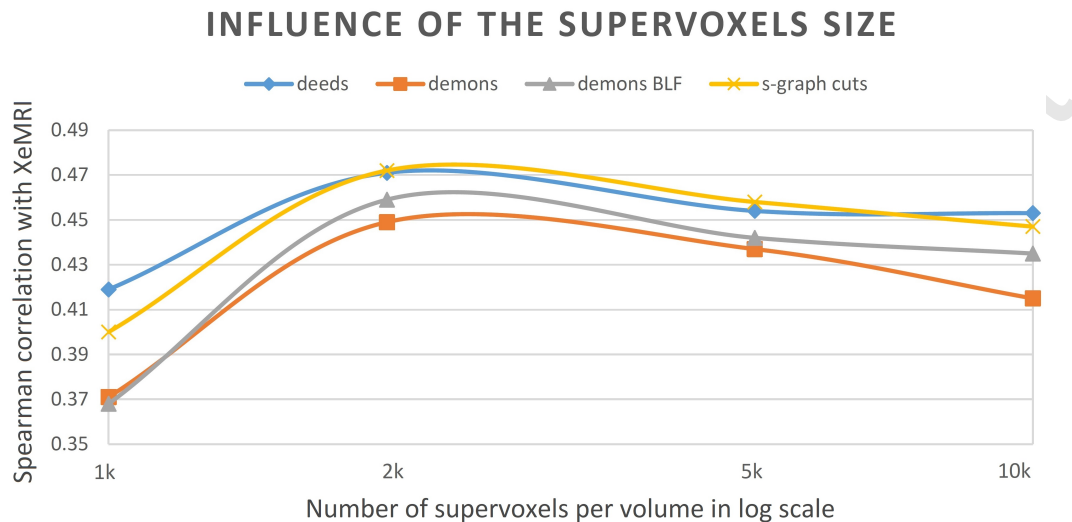


Figure 3: The plot shows the influence of the size of the supervoxels on the correlation of the estimated ventilation maps for all four registration methods with XeMRI ventilation images. The x-axis with supervoxel size is shown on a logarithmic scale. It is noticeable that for a low number of supervoxels the correlation is relatively low, then it reaches its maximum at approximately 2,000 supervoxels. The correlation gradually decays or reaches the plateau after further increasing the number of supervoxels.

387 3.2. Influence of the supervoxel size

388 The size of the supervoxels is one of the factors that have an influence
 389 on the results of the estimated ventilation maps. On the one hand, su-
 390 pervoxels that are too large may not be capable of modeling the regional
 391 nature of the ventilation changes. On the other hand, if too small, the su-
 392 pervoxels might lose their structure-oriented properties and provide similar
 393 results to the voxel-wise approaches. The purpose of this experiment is to
 394 investigate how the size of the supervoxels influences the correlation of the
 395 estimated ventilation maps with XeMRI ventilation images, and if there is
 396 a local maximum indicating an optimal size of the supervoxels. To investi-
 397 gate these properties, we have measured the correlation of the SLIC-based

398 estimated ventilation maps with XeMRI using different supervoxel sizes. We
399 have extracted approximately 1,000, 2,000, 5,000 and 10,000 of supervoxels
400 from each volume. The experiments were conducted with a fixed number of
401 supervoxel layers, namely 15, which is a reasonable trade-off between per-
402 formance and computational requirements. We have performed the same
403 experiment for all of the registration methods. In Fig. 3 we present a plot
404 showing the trend for average results on a logarithmic scale. The detailed
405 results for each individual case are presented in Appendix A.

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

413 *3.3. Influence of the number of layers*

414 The number of layers of supervoxels has an obvious influence on the esti-
415 mated ventilation images. Using just a single layer of supervoxels, the results
416 might be biased by the particular image clustering. By applying a larger
417 number of layers, the results should be more robust and we would expect the
418 correlation with XeMRI to be higher. We conducted an experiment investi-
419 gating the influence of the number of layers of supervoxels on the correlation
420 between the estimated ventilation maps with XeMRI for all four image regis-
421 tration methods. We estimated ventilation maps for 1, 5, 10, 15 and 25 layers
422 of supervoxels. The size of the supervoxels was adjusted based on the previ-

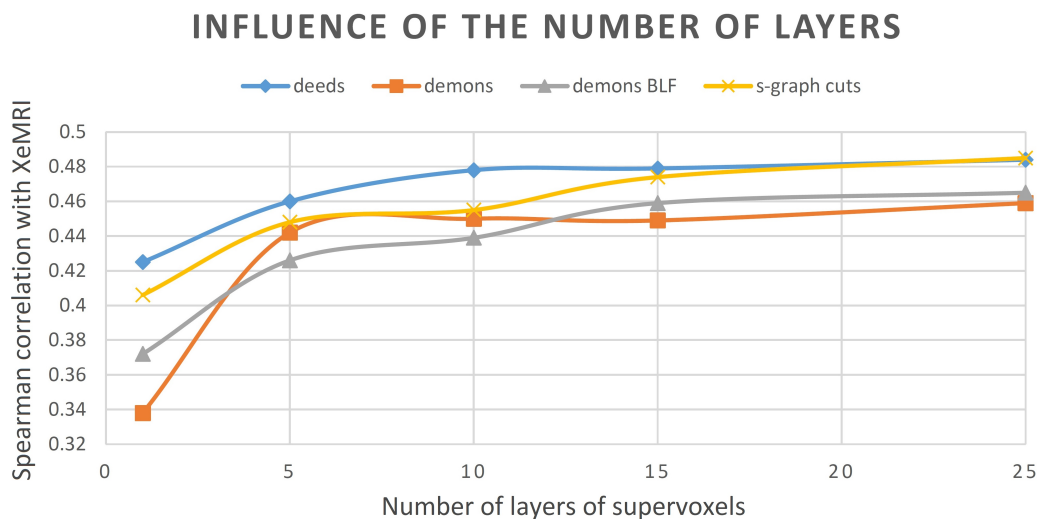


Figure 4: The plot shows the influence of the number of supervoxel layers on the correlation of the estimated ventilation maps with XeMRI ventilation images for all four registration methods. The correlation improves when the number of layers is increased, reaching a plateau for 25 layers.

423 ous experiment to approximately 2k supervoxels per volume. The obtained
 424 average results are shown in Fig. 4. The detailed results for each individual
 425 case are presented in Appendix B. The proposed method achieves relatively
 426 low correlation when there is just one layer of supervoxels. The results im-
 427 prove noticeably after increasing the number of layers to 5 layers, while there
 428 is a more gradual improvement up to 15. With the use of more than 15
 429 layers of supervoxels the correlation between XeMRI and the investigated
 430 ventilation surrogates estimated using different image registration methods
 431 reaches a plateau, with only slight improvement for 25 layers. Similar trends
 432 can be observed independently of the applied registration method.

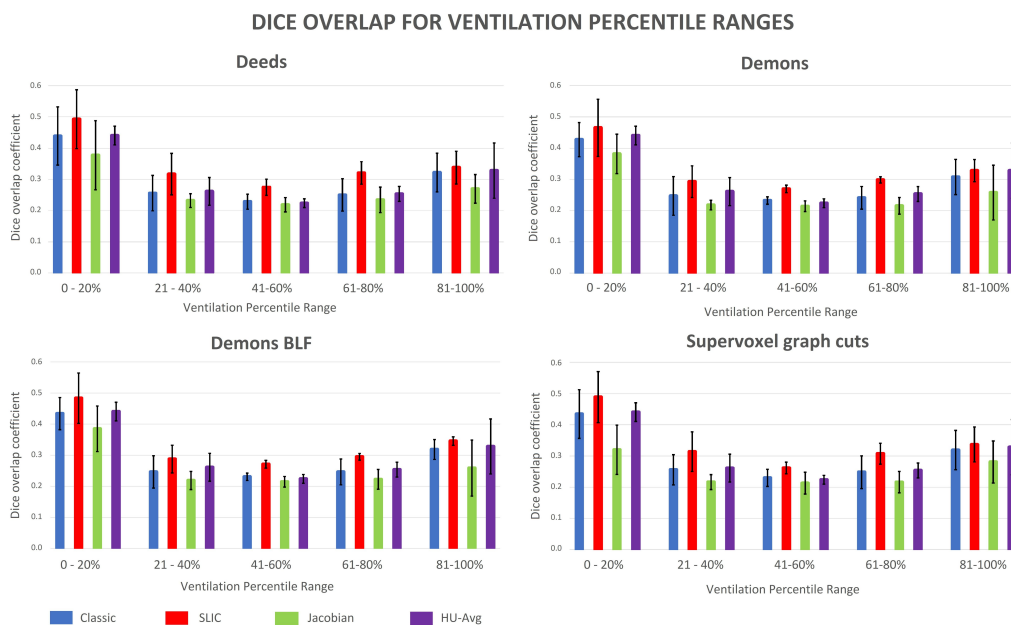


Figure 5: Dice overlap coefficient calculated for masks created based on the ventilation percentile ranges. We investigate the results for all four image registration methods: deeds, demons, demons with BLF and supervoxel graph cuts. For each of them we calculate all four estimates of the ventilation. 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.

Pat. no.	Classic				SLIC				Jacobian				HU-Avg
	demons	demons BLF	deeds	graph cuts	demons	demons BLF	deeds	graph cuts	demons	demons BLF	deeds	graph cuts	no reg.
1	0.205	0.306	0.356	0.348	0.369	0.426	0.476	0.477	0.274	0.273	0.280	0.278	0.399
2	0.605	0.598	0.645	0.633	0.667	0.656	0.690	0.678	0.335	0.349	0.414	0.339	0.444
3	0.279	0.256	0.186	0.198	0.332	0.313	0.287	0.299	0.096	0.105	0.109	0.101	0.315
Avg	0.363	0.386	0.396	0.393	0.459	0.465	0.484	0.485	0.235	0.242	0.268	0.231	0.386

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

452 In this experiment, we achieved a higher correlation for our method com-
453 pared with the others, when applied voxel-wise manner on average for all
454 cases. The best results were obtained independently of the chosen image
455 registration method. The classic approach achieved higher correlation com-
456 pared with HU averaging method for all image registration methods, apart
457 from the classic demons method. The lowest correlations with XeMRI were

458 obtained for the Jacobian-based method for all registration methods. Only
459 for this ventilation estimation approach, demons BLF achieved higher corre-
460 lation than supervoxel graph cuts for one of the cases, yet still lower than the
461 deeds method. The numerical results are presented in Table 1. Visualization
462 of the estimated ventilation maps for one of the cases is shown in Fig. 2.

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

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

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

479 *3.5. Spatial overlap comparison*

480 We have performed a series of experiments investigating the quantitative
481 relation between the spatial distribution of the estimated ventilation maps
482 and XeMRI ventilation images. Akin to [59], we have divided the estimated

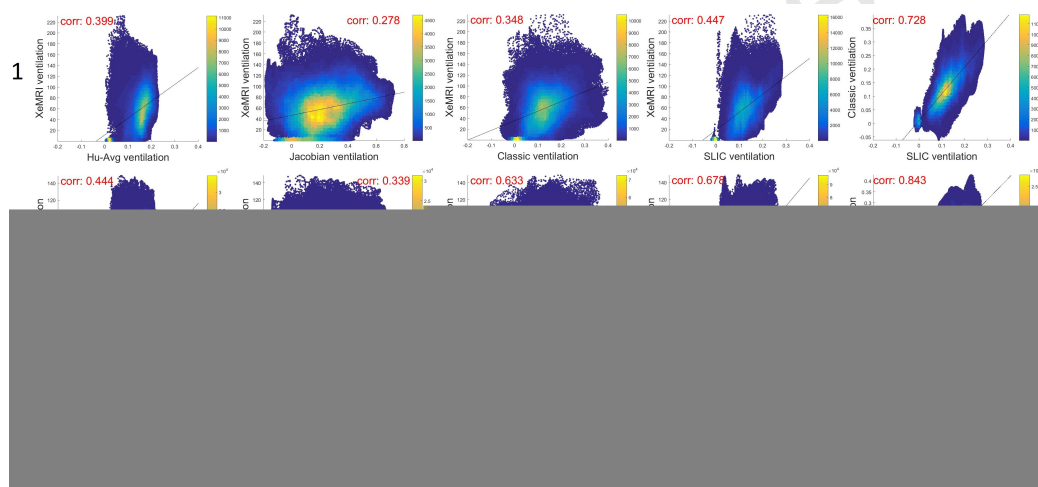


Figure 6: The figure shows correlation and Spearman correlation coefficient between the HU averaging ventilation approach and XeMRI in the first column. In the second column, correlation and Spearman correlation coefficient between the Jacobian-based ventilation approach and XeMRI are presented. In the 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.

483 ventilation images into five disjoint regions, based on calculated percentile
484 distribution ranges. These regions were further used to create masks corre-
485 sponding to the percentile ranges. For each of them, we calculated the Dice
486 overlap coefficient with corresponding masks of XeMRI. We have applied this
487 procedure to all four lung ventilation estimation methods and repeated the
488 experiments for all investigated image registration approaches.

489 The visualization of the results is presented in Fig. 5. The general trend,
490 where Dice overlap is the highest for the first percentile range (0-20%), for the
491 intermediate ranges is lower, and then raises for the last percentile range (81-
492 100%) is in agreement with similar experiments in the literature [59]. Similar
493 patterns in the results can be observed for all of the tested image registration
494 methods. For all of the evaluated percentile ranges, the highest correlation
495 has been achieved for our proposed method (in red). The lowest Dice overlap
496 has been obtained for the Jacobian-based ventilation method. The classic
497 approach and HU averaging method achieved similar results. The results for
498 the HU averaging method are independent of the image registration methods.
499 However, we decided to include them in the plots showing the results of the
500 correlation for different image registration methods to enable the comparison
501 with them.

502 **4. Discussion and Conclusions**

503 In this work, we have introduced and investigated the patch-based ap-
504 proach for ventilation estimation. We have conducted a number of exper-
505 iments, measuring the correlation of the estimated ventilation maps with
506 XeMRI ventilation images. To perform this evaluation, we have proposed

507 a registration framework to bring SLIC-based ventilation images into align-
508 ment with XeMRI. The presented results show that the proposed method
509 results in higher correlation with XeMRI for a number of performed tests.

510 We have investigated the influence of the supervoxel size in Sec. 3.2 for
511 all of the image registration methods. In the results presented in Fig. 3 we
512 can observe that to achieve the best correlation the size of the supervoxel
513 needs to be chosen with care. In our experiments we have found out that the
514 highest correlation has been achieved for approximately 2,000 supervoxels per
515 volume. This means that the average supervoxel consists of 30,000 isotropic
516 $1 \times 1 \times 1 \text{mm}^3$ voxels. This is related to their ability to model the anatomy of
517 the lungs. This trend in the changes of correlation has been expected and
518 supports our claim that structure-oriented patch-based approach is a better
519 choice than a voxel-wise approach. The limited number of available cases did
520 not allow us to create separate training and testing datasets. Apart from the
521 image registration methods settings, all other parameters of the presented
522 ventilation estimation method were trained and tested with the use of the
523 available dataset in a manner described in Materials section. The chosen
524 approach might be seen as suboptimal, however due to the unique character
525 of the dataset, creation of the separate training and testing datasets based
526 on them was not feasible. Further evaluation on the larger dataset would be
527 required to draw meaningful conclusions about superiority of the proposed
528 method compared to other approaches.

529 The results from Sec. 3.3 show that a larger number of layers of super-
530 voxels provides images more correlated with XeMRI. This is expected, as
531 a larger number of layers of supervoxels should improve the robustness of

532 the method for mis-segmentations originating from a particular supervoxel
533 extraction. In our work we have not investigated the influence of the com-
534 pactness of supervoxels because the intention is for the supervoxels to mimic
535 the anatomy of the lungs. Therefore, this parameter was adjusted manually
536 to make the supervoxels correspond in shape to lung structures.

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

549 The results presented in Sec. 3.4, where the classic demons image reg-
550 istration method was compared with its sliding motion preserving version,
551 show that the incorporation of the sliding motion improves the correlation of
552 the estimated ventilation maps with XeMRI. This observation supports the
553 claim that sliding motion preservation results in more anatomically plausi-
554 ble deformations of the registration. The deeds [44] and supervoxel graph
555 cuts [46] methods showed slightly more accurate performance on the Dir-Lab
556 dataset [52] than both demons methods, which is also reflected in the higher

557 correlations calculated for these methods. The difference between the cor-
558 relations calculated for the deeds [44] and supervoxel graph cuts [46] for all
559 ventilation estimation methods is minimal (below 0.01). This might suggest
560 that even though both methods represent different approaches to the image
561 registration problem, both cope well with the task providing similar level of
562 accuracy. This also suggests that more accurate image registration methods
563 provide estimations of ventilation which result in higher levels of correlation
564 with XeMRI.

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

574 In our work we have investigated the influence on the correlation of the
575 estimated ventilation with XeMRI of using four different image registration
576 methods. They represent distinct approaches to the task, covering most of
577 the existing groups of methods. We did not aim to evaluate which of the regis-
578 tration methods performed best, but rather wanted to show the general trend
579 that the application of our supervoxel-based ventilation estimation improves
580 the correlation to XeMRI ventilation maps, irrespective of the underlying
581 image registration.

582 An open point for a discussion might be whether the achieved level of
583 correlation reaches the expectations and is applicable to enhance radiother-
584 apy. The proposed SLIC-based method and the classic approach were able
585 to identify severe ventilation defects, as shows an example in Fig. 2. Precise
586 localization of the ventilation defects remains challenging to evaluate. In a
587 recent study [66], the researchers have evaluated and compared ventilation
588 maps estimated on 4DCT and high quality exhale/inhale breath-hold CT
589 (BHCT) with Galligas PET. They found that ventilation maps estimated
590 using BHCT achieved higher correlation values. Such an observation may be
591 mainly due to reconstruction artifacts present in 4DCT, and could suggest
592 that the application of BHCT has the potential to improve the accuracy of
593 the estimated ventilation maps. Additionally, in our opinion an improved
594 pMRI to CT registration, which brings XeMRI to the alignment with CT,
595 plays an important role in this evaluation. The method applied in our study,
596 as well as methods applied by other researchers were not developed strictly
597 for this task. Therefore, the pattern of the regularization applied inside of
598 the lungs might not be fully corresponding with the anatomy of the lungs.

599 A detailed analysis including a larger group of patients could further
600 support our results. The presented results, where for the majority of the
601 conducted experiments the proposed method for ventilation estimation from
602 4DCT achieves better correlations with XeMRI images, indicate higher phys-
603 iological consistency of our proposed approach using supervoxels for ventila-
604 tion estimation. In future, we are planning to perform further analysis on
605 a larger patient group. Another crucial issue is XeMRI to CT registration.
606 We could observe the improvement in the correlation for more accurate im-

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

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

618 **Conflict of interest**

619 The authors have no conflict of interest to disclose.

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852 **Appendix A Influence of the supervoxel size**

853 Here, we present detailed numerical results calculated for the influence of
 854 the supervoxels size, based on which plots from Fig. 3 were prepared. The
 855 provided Tables 2, 3, 4, 5 were used to create Fig. 3, where we investigate
 856 the influence of the supervoxel size on the Spearman correlation between the
 857 results of the proposed estimated ventilation method and XeMRI ventilation
 858 images. In Tables 2, 3, 4, 5 we have shown the results calculated for the
 859 different image registration methods, the deeds [44], demons [45], BLF [41]
 860 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.

Patient	~ 1k	~ 2k	~ 5k	~ 10k
1	0.364	0.471	0.421	0.423
2	0.686	0.685	0.678	0.677
3	0.209	0.282	0.263	0.259
Avg	0.419	0.479	0.454	0.453

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.

Patient	~ 1k	~ 2k	~ 5k	~ 10k
1	0.220	0.351	0.336	0.302
2	0.639	0.661	0.660	0.651
3	0.255	0.336	0.315	0.292
Avg	0.371	0.449	0.437	0.415

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.

Patient	~ 1k	~ 2k	~ 5k	~ 10k
1	0.236	0.417	0.380	0.372
2	0.651	0.653	0.650	0.641
3	0.218	0.308	0.295	0.294
Avg	0.368	0.459	0.442	0.435

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.

Patient	~ 1k	~ 2k	~ 5k	~ 10k
1	0.385	0.450	0.428	0.417
2	0.603	0.675	0.667	0.659
3	0.213	0.298	0.278	0.264
Avg	0.400	0.474	0.458	0.447

861 Appendix B Influence of the number of supervoxel layers

862 We present here detailed numerical results calculated for the influence of
 863 the number of supervoxels layers on Spearman correlation between estimated
 864 ventilation surrogates and XeMRI, based on which plots from Fig. 4 were
 865 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.

Patient	1 layer	5 layers	10 layers	15 layers	25 layers
1	0.374	0.411	0.469	0.471	0.476
2	0.644	0.689	0.686	0.685	0.690
3	0.257	0.281	0.280	0.282	0.287
Avg	0.425	0.460	0.478	0.479	0.484

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.

Patient	1 layer	5 layers	10 layers	15 layers	25 layers
1	0.200	0.326	0.354	0.351	0.369
2	0.500	0.662	0.663	0.661	0.667
3	0.315	0.338	0.335	0.336	0.332
Avg	0.338	0.442	0.450	0.449	0.459

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 .

Patient	1 layer	5 layer	10 layer	15 layers	25 layers
1	0.254	0.334	0.361	0.417	0.426
2	0.562	0.638	0.653	0.653	0.656
3	0.300	0.308	0.302	0.308	0.313
Avg	0.372	0.426	0.439	0.459	0.465

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.

Patient	1 layer	5 layer	10 layer	15 layers	25 layers
1	0.291	0.377	0.398	0.450	0.477
2	0.652	0.677	0.671	0.675	0.678
3	0.275	0.289	0.297	0.298	0.299
Avg	0.406	0.448	0.455	0.474	0.485

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 exhale breathing 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.

