PhD Research Project
2024-2027

Project title

Fast lung segmentation and registration to assess local ventilation from computerized tomography images of patients with acute respiratory distress syndrome

Laboratory

CREATIS, CNRS UMR 5220 – INSERM U1294 – Université Claude Bernard Lyon 1, INSA Lyon
21, Avenue Jean Capelle, 69100 Villeurbanne
Laboratory director: Prof. Olivier BEUF

Project supervisors

Prof. Maciej ORKISZ, PhD
CREATIS, team MYRIAD
Université Claude Bernard Lyon 1
Tel: +33 4 72 43 60 58
Mail: maciej.orkisz@creatis.insa-lyon.fr

Emmanuel ROUX, PhD
CREATIS, team MYRIAD
Université Claude Bernard Lyon 1
Tel: +33 4 72 43 60 58
Mail: emmanuel.roux@creatis.insa-lyon.fr

Co-advisors

Prof. Jean-Christophe RICHARD, MD, PhD
Service de Médecine Intensive – Réanimation
Hôpital de la Croix Rousse, Hospices Civils de Lyon
103, Grande Rue de la Croix Rousse, 69004 Lyon
Tel: +33 4 26 10 94 93
Mail: j-christophe.richard@chu-lyon.fr

Dr. Laurent BITKER, MD, PhD
Service de Médecine Intensive – Réanimation
Hôpital de la Croix Rousse, Hospices Civils de Lyon
103, Grande Rue de la Croix Rousse, 69004 Lyon
Tel: +33 4 26 10 94 93
Mail: laurent.bitker@chu-lyon.fr

Summary

The project will tackle the lack of fast and reliable tools to personalize the artificial ventilation settings for patients with acute respiratory distress syndrome (ARDS). These patients need artificial ventilation to survive while the cause of the disease is treated, but inappropriate settings can increase mortality, and clinicians lack tools to assess the response of the patient's lungs to artificial ventilation. Lung aeration maps and biomarkers useful for the clinicians, such as alveolar recruitment and hyperinflation, can be extracted from pairs (e.g., inspiratory/expiratory) of 3D chest computed tomography (CT) images, provided accurate lung segmentation and registration methods are available, but conventional algorithms fail due to the lack of contrast typical of ARDS. Yet, thanks to our partnerships with physicians and the resulting access to unique annotated databases, we have recently shown that deep learning methods can successfully perform these tasks. Our aim today is to make our models available to intensive care units, which requires to make them more robust, and to guarantee their high performance, whatever CT scanner is used. To achieve this, the project aims to improve the generalizability of the models by both optimizing the learning strategy (domain adaptation) and diversifying the database. Prior knowledge of the lung shape will be introduced *via* a parametric model based on spectral shape analysis, and a new method will be developed for generating numerous ultra-realistic image pairs with ground-truth lung shape and deformations. These hybrid images will combine thorax morphologies and lung masks from easy-to-segment images of patients without ARDS, on the one hand, and lung lesions, heterogeneous deformations and density changes learned from patients with ARDS, on the other. The models will be implemented in a graphical interface for use in clinical trials aiming to propose and validate image-assisted ventilation strategies and, ultimately, reduce patient mortality.

Highlights

Strong partnership with clinicians.

Solid experience of the team in the targeted application and methodology areas.

Contractual access to unique and still growing databases of 3D CT thoracic scans with carefully segmented lungs, for learning and evaluation.

Prospects for clinical use of the methodology developed and, ultimately, reduced patient mortality.

Background

Acute respiratory distress syndrome (ARDS) is a serious lung disease that accounts for 4-10% of admissions to the intensive care units and has a very high mortality rate (30-50%). Massive loss of pulmonary aeration requires patients to be placed on mechanical ventilation, but this can cause further damage known as ventilation-induced lung injury (VILI) and excess mortality, particularly if its settings are not appropriately personalized. To date, clinicians have no reliable rapid means of measuring lung tolerance to mechanical ventilation.

Computed tomography (CT) provides an image of tissue density, which – in the case of lung parenchyma – can be related to aeration. Thus, 3D CT thoracic scans can be used to assess lung response to artificial ventilation, notably by measuring alveolar recruitment (re-aeration) and pulmonary hyperinflation (excess of air insufflated by the ventilator into already aerated regions). To achieve this, the lungs must be separated from the other intrathoracic tissues visualized on the CT image. This process, known as lung segmentation, is unfortunately not feasible in clinical practice, as manual segmentation takes several hours, while the automatic methods currently available for lung segmentation are only suitable for high-contrast lungs (with little pathology or small focal lesions). Indeed, they fail in ARDS patients, whose CT images show very little or no contrast with neighboring structures due to the dense (very diseased and therefore non-aerated) areas typical of this syndrome. It is therefore necessary to provide clinicians with robust, easy-to-use software capable of performing lung segmentation and aeration quantification within minutes, despite contrast loss.

For the past dozen of years, our team has been conducting research on CT image analysis in ARDS from both medical and image-processing standpoints. The best results have been recently obtained using a segmentation method based on artificial intelligence, namely on an artificial neural network called 3D U-net. The algorithm, trained on 316 annotated 3D CT scans from 97 patients and evaluated on 118 scans from 34 patients with moderate-to-severe ARDS, achieved high overlap (96% Dice score) and low average surface distance (1.2mm ASSD) compared with reference annotations [Peñarrubia, PhD thesis 2022]. Its uncertainties are on the order of inter-observer variability [Peñarrubia, *et al*. ICMX 2023] and our clinical partners from the Croix Rousse hospital estimate that 85% of the automatically segmented lung masks are exploitable. We target a multi-centric observational study, using a prototype software implementing this algorithm, to make a proof-of-concept of image-assisted ventilation.

Nevertheless, wider deployment of the software requires an improvement in the algorithm's robustness, while guaranteeing high accuracy, irrespective of the scanner brand used in the hospital concerned. Furthermore, lung segmentation allows assessing biomarkers of interest (recruitment and hyperinflation) globally, for the whole lungs, whereas pathological changes and the resulting lung response to mechanical ventilation are heterogeneous. This heterogeneity leads to high local mechanical stresses and strains, which in turn cause additional damage leading to VILI. Assessment of local lung response to mechanical ventilation requires not only segmentation but also alignment of lung tissues between CT scans acquired at different conditions (e.g., exhale/inhale or different positive end-expiratory pressures, PEEP). This process, known as image registration, requires special care near motion discontinuities between lungs and thoracic cage and thus may benefit from accurate lung segmentation [Peñarrubia, *et al*. Med Phys 2022], but also may contribute to reduce segmentation errors [Orkisz, *et al*. IJCARS 2019].

Keywords: acute respiratory distress syndrome, computed tomography ventilation imaging, image processing, image segmentation, image registration, artificial intelligence, deep learning

Objectives, scientific challenges and expected original contributions

Objectives: The main objective of this project is to develop and validate a clinically usable methodology for assessing local changes in lung parenchymal aeration between CT scans acquired under different conditions. To be clinically usable, results must be available within minutes and robust to large variability factors, namely: patients' morphologies, heterogeneous lesion patterns, as well as image characteristics specific to different scanner manufacturers.

To this end, several auxiliary objectives will be addressed:

- Improve the robustness and accuracy of the automatic segmentation process.
- Develop a fast and accurate image registration method adapted to CT scans with ARDS.
- Validate the proposed methodology on a relevant database.

Challenges: As the high-density ARDS lesions strongly blur the contrasts between the lungs and other tissues, precise delineation of the lungs is a challenge even for human experts. Consequently, the reliability of annotations used for training and evaluation is limited.

The amount of annotated data for training and evaluation is also very limited, compared to the typical requirements of deep-learning algorithms.

The CT scanners in Lyon hospitals are all Philips-branded, which prevents the creation of a balanced database representing CT scanners from different manufacturers.

Image registration of lung CT scans is challenging, even in healthy subjects, due to changes in tissue density between different respiratory phases and motion discontinuities across the pleural interface. Accounting for these specificities leads to time-consuming approaches. ARDS cases are even more challenging, as the contrasts are decreased and the changes in density are heterogeneous reflecting locally different physiological phenomena (normal changes in air content, recruitment, hyperinflation).

An additional challenge in developing an accurate registration method for these images is the lack of ground truth on tissue deformation.

Contributions: In line with the objectives and challenges, several original contributions are expected:

- A learning strategy that withstands imbalance between the numbers of images from different scanner brands.
- A deep-learning model trained according to this strategy to segment the lungs robustly and accurately in CT scans of patients with moderate-to-severe ARDS.
- A new image registration algorithm adapted to the specificities of thoracic CT and capable of aligning lung structures with millimetric precision in a matter of minutes.
- A large database with reference annotations allowing the validation of both lung segmentation and registration processes.

Research program and proposed scientific approach

To achieve the ambitious goals of the project, the PhD student will explore several avenues.

Firstly, using the current U-net 3D architecture and the already available database CT4ARDS-2 (clinicalTrials NCT06113276), which contains four annotated CT scans per patient for over 160 patients and continues to grow, the student will focus on optimizing the learning strategy for lung segmentation. This phase will include the search for more relevant loss functions and the introduction of prior knowledge of lung shape via a parametric model (mesh) based on the paradigm of spectral shape analysis [Márquez Sosa M., *et al.*, IABM 2024]. The latter will be used to regularize the solution and thus avoid outliers corresponding to the unexploitable results (15%) obtained by the current model.

In parallel, images acquired by scanners of various brands will be collected and annotated thanks to our collaborations and partnerships in France and abroad. These data will enable us to improve the generalizability of the model by data diversification, but also to "desensitize" it to scanner-specific image features. Using domain adaptation techniques [Guan and Liu, TBME 2022], the PhD student will train the model to predict the shape of the lungs in the image without being able to classify from latent space which manufacturer the image comes from.

To overcome the scarcity of available annotated data from ARDS patients, and increase the diversity of lung morphologies, we also foresee an original solution for data augmentation. The PhD student will propose a method to generate ultra-realistic synthetic CT scans by incorporating ARDS lesions seamlessly [Shen and Li IEEE IUS 2023; Bai, *et al*. CVPR 2023] (without creating perceptible boundaries) into normal lungs and, for each synthetic CT scan thus generated, simulate heterogeneous inflation by modifying local volumes and densities. The underlying idea is that CT scans from various brands representing normally-contrasted lungs are way easier to collect and annotate (e.g., they can be segmented using existing software such as TotalSegmentator [Wasserthal J. *et al*. Radiology 2023]), whereas heterogeneous aeration patterns, as well as lesions of varying extent, density, and location, can be learned from patients with ARDS. This approach will allow generating an ARDS CT-lung database with an unprecedented diversity of lesions and aeration patterns, with ground truth for both training and evaluation purposes.

As the image pairs thus generated will be linked together by a perfectly known spatial transformation, the resulting database will become the cornerstone of work aiming to develop an efficient image registration algorithm for our application. This work will build on a new artificial neural network architecture proposed as part of a PhD project defended very recently in our team [Shekarnabi, PhD thesis 2023]. This network performs a multitask processing of CT-scan pairs, in which lung segmentation and registration are achieved jointly. While its segmentation performance is very promising, image registration – learned in an unsupervised manner in the absence of ground truth – has not yet been assessed quantitatively. Moreover, further investigation is necessary to improve several features of this model to make it usable in clinical practice. Its current main limitation is its high computational demand, which slows down the learning process and complicates experimentation with different parameters and configurations. This is because the registration task is solved in the volumetric image space; a solution could be to use a network graph neural networks operating on meshes which is much lighter than image-based features [Schneider, et al. CMPB 2021]. The first step of the investigation will be an ablation study to assess the importance of each network component and propose simplifications to the architecture while maintaining high performance. Subsequently, the benefits of the previously optimized learning strategy will be evaluated for this model.

Scientific supervision, integration within the laboratory (teams/projects, external collaborations/partnerships)

The project supervisors have complementary experience in the medical field (Prof. J.-C. Richard, expert in intensive care with a particular focus on ARDS) and in artificial intelligence (E. Roux, expert in deep learning, involved in the investigation of ARDS for the past three years). The PhD student can count on co-advisors experienced in research on ARDS from medical (Dr. L. Bitker) and image-processing (Prof. M. Orkisz) standpoints.

Within CREATIS laboratory, the student will be integrated into the MYRIAD team (Modeling & analysis for medical imaging and diagnosis) and the transversal project FILM (Functional Imaging and Modelling of Lungs, leader M. Orkisz), with which all supervisors and co-advisors are affiliated.

Furthermore, the project will be carried out in close local collaboration with the Intensive Care Unit of the Croix Rousse hospital, Lyon (head: J.-C. Richard), as well as in national collaboration with the Intensive Care Unit at Hôpital de Brabois, Nancy (Dr. Benjamin Pequignot) and with STROBE laboratory and Alpes University Hospital, Grenoble (Prof. Sam Bayat).

Our international partnership (ARQUS program) with the Klinik für Anästhesiologie, Intensivmedizin, Notfallmedizin und Schmerztherapie, Zwickau, Germany (Prof. Andreas Reske) will be a major source of expertise and annotated images.

Candidate's profile (prerequisites)

Image processing, applied mathematics, programming (python), deep learning (PyTorch)

Skills to be developed during the thesis and professional prospects

In-depth knowledge of image processing and artificial intelligence techniques.
Biomedical knowledge acquisition.
IT project management (versioning, collaborative development…).
Developing human qualities: dialogue with the medical community.
Prospects in both public and industrial research, as well as in engineering fields such as data science or AI-based software development, particularly for medical applications.

Objectives for promoting research work

The aim of the project is to provide clinicians with a reliable and rapid tool for assessing the response of the patient's lungs to mechanical ventilation, using maps of lung parenchymal aeration change calculated from CT images and biomarkers derived thereof. This tool will be used in multi-center clinical trials designed to propose and validate image-driven ventilation strategies enabling personalized treatment to minimize ventilation-induced lung injury and, ultimately, reduce mortality. To this end, the algorithms and models developed by the PhD student will be implemented in end-user software co-developed either with a company manufacturing medical equipment (scanners or ventilators), or with a provider of artificial intelligence solutions for medical applications. Anticipating this technology transfer, we have enlisted the help of SATT PULSALYS to find suitable industrial partners. Appropriate intellectual property protection will also be sought with this in mind. Nevertheless, insofar as publications remain compatible with this endeavor, methodological innovations will be published in scientific journals.

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