

## Building of a computational lung for studying pulmonary diseases

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Aida Perramon<sup>1</sup> and Inma Villanueva<sup>2</sup>

<sup>1,2</sup>*Polytechnic University of Catalonia, Barcelona, Engineering Physics  
Campus Nord, Carrer de Jordi Girona, 1, 3, Barcelona, Spain 08034*

<sup>1</sup>*e-mail address: [aida.perramon@estudiant.upc.edu](mailto:aida.perramon@estudiant.upc.edu)*

<sup>2</sup>*e-mail address: [m.inmaculada.villanueva@estudiant.upc.edu](mailto:m.inmaculada.villanueva@estudiant.upc.edu)*

For the sake of reducing animal experimentation and acting according to the principles of the 3Rs, the aim of this project has been to create a virtual lung using CT images as a template and MATLAB as a tool of image processing and analysis, for a future implementation of pulmonary diseases' models. From the study of the CTs to do the 3D reconstruction, data of medical relevance have been obtained with the perspective to be useful to improve the mathematical models that nowadays describe different diseases.

**Keywords:** Computational lung, Virtual lung, MATLAB, CT images, Pulmonary diseases, Carina

### I. INTRODUCTION

Lung diseases are one of the biggest problems for global health [1]; chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis and lung cancer are leading causes of death and disability in the world [2]. Prevention, control and cure of these diseases are a top priority in the health sector. Therefore, there is a considerable investment and interest in studies related to this topic.

In biomedical research there are three broad categories of studies: *in vitro*, *in vivo* and *in silico* [2]. An *in vitro* experiment is the one performed in laboratory culturing devices using tissues, cells or molecules from animal species, while *in vivo* experiments are those carried out with animal species. On the other hand, *in silico* experiments are simulations or reproductions of *in vitro* or *in vivo* experiments, using mathematical models and simulation software. They are a useful tool in the framework of the 3Rs' principles (Replacement, Reduction and Refinement) [4], which were developed over 50 years ago establishing accepted standards to investigate with animals.

Since then, those principles have been incorporated into national and international legislation and regulations on the use of animals in scientific procedures, as well as in the policies of organizations that fund or carry out animal research [5]. The 3Rs promote the minimisation of the number of animals used per study and the pain they may experience, and also the development and use of alternative models (e.g., *in silico* models) and tools to avoid the use of animals in experiments [6].

The objective of this paper is to explain the procedure of creating an automatized MATLAB code for the building of a virtual lung in which pulmonary disease's models can be later implemented, e.g. to understand and test hypotheses about the dynamics of lung diseases or to study pulmonary

affections. In order to do so, human computed tomography (CT) images are used to build a 3D reconstruction of lungs and trachea. Tomography offers excellent spatial morphological information. Lungs structure may be relevant to the development of a pulmonary disease. The more precise the information is, the better the reconstruction and the more useful for *in silico* studies.

### II. METHODS

After some research, CTs from 675 cancer patients were downloaded from Cancer Imaging Archive [7] and for each one a folder named "Pacient n - m" was created, n being de number of the patient and m being the number of CT images in the folder. Then, a MATLAB algorithm was designed for automatically analyse the CT images of a certain patient and build the corresponding computational lung. The details of the algorithm are explained below, and the complete process is summarized in Figure 1.

In the MATLAB code, a patient's folder is introduced as an input and new folders inside that one are created to save new black and white ".png" images that will be generated.

To process all images, the Image Segmenter App is used [8]. First, a threshold of 420 and a binary mask are applied, so all pixels with a pixel intensity lower than that value are shown as 0s, and those with a pixel intensity higher than 420, as 1s. Then, the mask is inverted, so all 0s change to 1s and viceversa; thus, lungs, trachea and other areas change to 1s. Afterwards, borders are cleared to remove small regions on the edge of the images, and holes in the foreground regions are filled. Finally, an open mask with octagons of radius 3 pixels, a morphology tool to fix slight imperfections that removes elements with a radius of less than 3 pixels and smooths the edges, is applied.

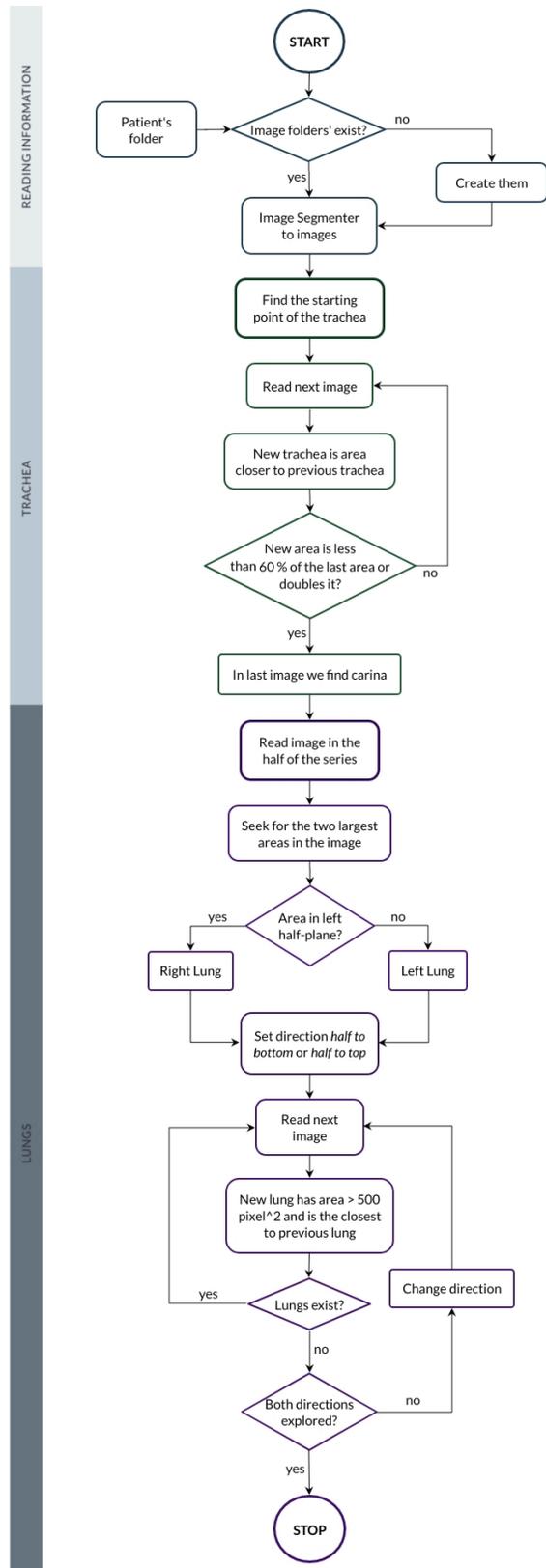


FIG. 1. Flowchart of the MATLAB code programmed.

The starting point of the trachea is found by identifying the first image with a single area larger than 30 pixels<sup>2</sup>. Moreover, a zero matrix of dimensions (x, y, z) is created, x and y being the size of the CT images, read from the first DICOM trachea image, and z being the number of images. For the following images, the different areas are distinguished and their distance to the previous image's trachea is calculated, being the one with the minimum distance the current trachea. Each image of the trachea is saved in the three dimensional matrix as 0s and 3s, and their centroid, area and equivalent diameter in the respective vectors. The carina (the point where the trachea joins the bronchi) is identified when there is a trachea's area that is less than 60% of the last area size or doubles it.

The first and last 20% of the diameters previously saved are neglected, and the resulting set is fitted to a first degree polynomial to calculate the slope. The average diameter of the trachea and its length are obtained calculating the arithmetic mean, multiplying by the resolution of the images so that the units are mm, and multiplying the number of diameters by the distance between CTs, respectively.

The bifurcation angle between the bronchi, distinguishing both of them, is obtained calculating the arctangent of the distance travelled by the bronchus from the image of the carina to the second image after the carina divided by the distance between images.

Regarding the lungs, in the middle image of the series the two biggest areas are identified, the one in the left being the right lung and the other one, the left lung, and their centroids and areas are saved. From this image to the last one and to the first one, all areas are distinguished, their centroids located and the distance to the previous lungs calculated. The area with the minimum distance to the previous left lung is the current left lung, and the one with the minimum distance to the right lung, the current right lung. When the area of a lung is lower than 500 pixel<sup>2</sup>, it is considered the end or starting point of the lung. If at any image it is detected that the biggest area is higher than the 95% of the total area, meaning that both lungs unite, it is separated approximately in half. Every image of the right lung is saved in the three dimensional matrix as 0s and 1s and all images of the left lung, as 0s and 2s.

Finally, when the matrix is completed, a morphological closure with a sphere of radius 3 pixels as structuring element is used just in the matrix of the lungs to fill volume holes' and help soften the edges of the lungs. Volume Viewer, a MATLAB's app, can be used to visualize the total three dimensional matrix.

The volume of the right and the left lung can be calculated counting the total number of 1s and 2s, respectively, and multiplying by the distance between CT images and their resolution.

### III. RESULTS

15 lungs are analysed and a perfect reconstruction is obtained in 8 of them (Fig. 2). Hence, the success percentage is of 53.33 %. Nonetheless, in 4 from the other 7, the problems found could be solved adjusting the conditions fixed, because it was noticed that the area recognition failed depending on the threshold and that some small areas were wrongly interpreted as if they were trachea or lungs. For the other 3, further study should be done to realise why there is no data obtention.

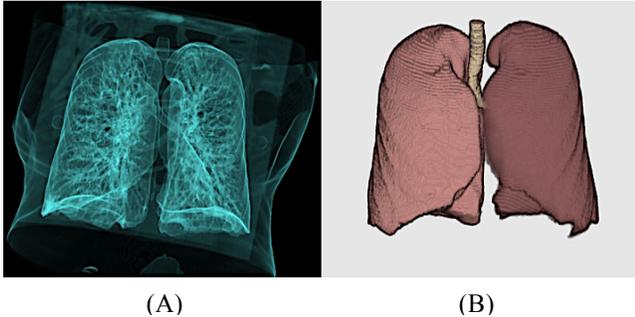


FIG. 2. 3D reconstruction of the lungs with RadiAnt DICOM Viewer software (A) compared to our code's reconstruction through the Volume Viewer app in MATLAB (B).

As it can be seen in figure 2, our reconstruction is almost identical to that made by medical software, but also including the trachea and with the possibility of exporting the data of pulmonary volume, trachea's diameter, angles of bifurcation of the first bronchi, and others calculated.

On the other hand, the positive results were not immediate. First of all, an adaptation of the code for the first patient's CTs was made. The threshold value was calibrated to avoid that the areas of the lungs joined in just one area, centroids were found to conditionate the acceptance of regions' identification and to abstain from using non-automatized conditions. Furthermore, a last stage for 3D filling of holes was introduced inasmuch as the irregularities in the contour of the areas were notorious and in some images from the bottom of the lungs one of them was divided into two because of the Image Segmenter effect. Thus, a 3D fill would compare images above and under to consequently join them where necessary.

For a further study of the reliability of the code with other patients, the process of reading images was also automatized, first being only necessary to introduce the name of the folder in which the CTs were and the sample number while later reading all the folders in the main directory automatically. After testing the script, we realized that the threshold adjustment was not enough to avoid the lungs joining so a divide function was introduced in the Image Segmenter.

Relevant data for future analysis and implementation of disease models has been obtained.

Patient	Trachea's length (mm)	Trachea's average diameter (mm)	Right bifurcation angle (deg)	Left bifurcation angle (deg)	Right lung's volume (litres)	Left lung's volume (litres)	Total volume (litres)
1	62.5	15.6	55.0	42.8	1.9	1.7	3.6
2	75.0	17.4	38.6	14.5	2.7	2.4	5.1
3	82.5	21.0	45.4	16.5	3.0	2.7	5.7
4	60.0	15.6	39.3	54.4	2.4	2.2	4.6
5	71.3	18.8	87.6	56.5	1.9	1.8	3.7
6	67.5	18.7	05.2	22.2	2.6	2.5	5.1
7	72.5	16.1	82.9	80.3	2.9	2.5	5.4
8	58.8	14.0	34.9	40.4	1.6	1.4	3.0
Average	68.8±8.1	17.2±2.3	48.6±26.7	41.0±22.8	2.4±0.5	2.2±0.5	4.5±0.9

TABLE 1. Table with anatomic information from the 8 patients for which the code success.

Results shown in table 1 allow us to speculate. The average total pulmonary volume in adult men is expected to be between 4 and 8 litres whereas in adult women the average stands between 2 and 4 litres according to [9]. Therefore, results in patients 1, 5 and 8 lead us to think their sex is female while for 2, 3, 6 and 7 one may conclude the lungs to be from a male subject. However, patient number 4 is an interesting case because it does not present conclusive results.

Another connection to sex we found, although less significant, is the length of the trachea and its average diameter. Females show a shorter and thinner trachea, about 60 mm long and with an average diameter about 15 mm, in contrast with the average 70 mm in length and 17 mm in thickness of males. As this could be a consequence of height and age [10], it is not determinant when it comes to fixing the patient's sex. Hence, one can speculate patient number 4 to be a short and thin adult men, even a child, or a woman with swollen lungs maybe for an obstructive disease (COPD) which is a risk factor of the cancer the patient has. Moreover, we may review the conclusion regarding patient number 5 because for its trachea anatomic conditions it could be labelled as a male subject even though the pulmonary volume corresponds to a female. However, the most reasonable conclusion is that the patient is a tall woman.

Comparing ours with other studies' results [11] as a reference, we see that although the sample is quite small the data obtained are coherent.

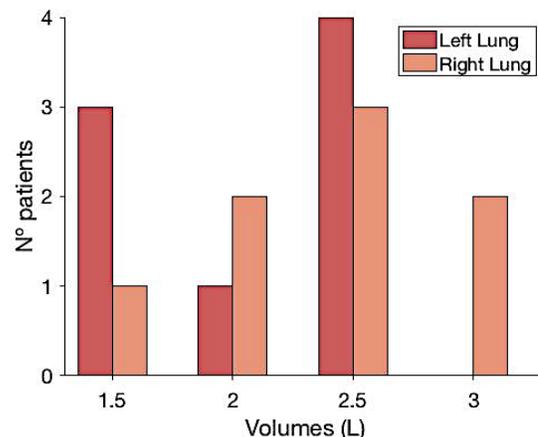


FIG. 3. Histogram for right and left pulmonary volumes.

From the histogram of figure 3 one may deduce that the average pulmonary volume concerning right lung for a subject in our sample is between 2 and 3 litres, which could correspond to the mean values of females and males, respectively. That makes an average of right lung's volume of 2.5 litres while the referenced stands in 2.51 litres. With respect to the left lung's volume, the average should be between 1.5 and 2.5 litres, being 2 litres, in contrast to the reference value of 2.43 litres, a difference that can be explained by the lack of samples. The average values calculated from the histograms are similar to those in table 1 and therefore it can be considered that the error made is negligible.

In addition, a comparison between the average total volume referenced of 5.05 litres [11] and the one obtained can also be made. The histogram of figure 4 shows a clear peak in 5 litres, therefore the average volume should be around there. Since there is a negligible error of 5 cl one can consider our results to be coherent and reliable.

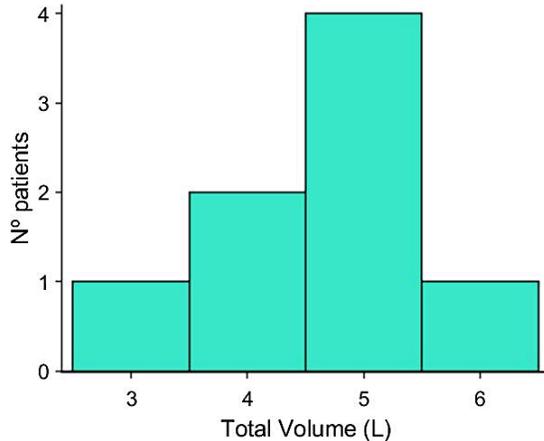


FIG. 4. Histogram for total pulmonary volumes.

In reference to the angles of the first bifurcation of the trachea to the bronchial tree, what can be deduced from table 1 and subsequent analysis is that there is no significant relation to the sex of the patient. Nevertheless, the larger the trachea the smaller the bifurcation angle.

Furthermore, taking into consideration that the total bifurcation angle should be around  $70^\circ$  [12], from table 1 we can see that from patients 5 and 7 unrealistic measures are obtained. However, the average total bifurcation angle is of  $89.6^\circ$  and considering that the two aberrant measures have not been neglected, the error committed is acceptable.

## IV. CONCLUSIONS

The results obtained, though they do not adjust perfectly to the theoretical values, are more than acceptable. Moreover, we have not only accomplished our goal of creating a computational lung, but managed to generate a code that works for 8 different lungs, successfully reconstructing their structure.

Besides, we are able to differentiate both lungs and determine their volume, trachea's diameter, length, and the relation between them; the location of the carina and the first bronchi's bifurcation angle from a series of CT images, obtaining reliable data useful for future implementation of diseases' models.

Nevertheless, there are still some details in which further work could be undertaken to improve the code. For instance, when calculating the bifurcation angles more images of the bronchi could be considered instead of stopping at the second one after the carina, which would reduce the error. Additionally, having a fairly large database, the code could be tested with all lungs in order to obtain more accurate results.

Finally, a function could be written so that when some point in space is introduced as an input, taking the carina as the origin of coordinates, it provides as an output the location of that point: if it is in the right lung, in the left lung or in the trachea. This could be useful for research in pulmonary diseases.

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