UNIVERSITY OF GIRONA

Final Project Report

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CONTENTS

1 INTRODUCTION

Medical images are increasingly being used within healthcare for diagnosis, planning treatment, guiding treatment and monitoring disease progression.In many of these studies, the images of a subject, are acquired in different time or in different modality. Furthermore often happens that most of human organs are non-rigid, such as lung, heart, liver, etc. So studies about non-rigid medical image registration of non-rigid image have important significance. Moreover it has to be notice that it is really important the comparison of different examination for evaluate the evolution of the disease. Hence, here medical registration image come into play.

Medical image registration technique is the basis and prerequisite of developing operation plan, image guided surgery, image-guided radiotherapy, medical image fusion processing and postoperative effect evaluation and so on, which has important clinical application value.

There are various registration algorithms in the field of medical image registration, based on the different features calculated of registration algorithm. Registration algorithm can be divided mainly into:

feature-based registration algorithm. In order to registered pair of images, features such as key point (point linear contour curve and surface features), are extract and matched. When the matching is done the next step is the computation of the optimal registration parameters by using the relationship between the feature sets. Due to some advantages, such as that the parameter are computed on a reduced number of point respect to the size of the image, this algorithm has an high efficacy on converge to the optimal transformation value. However, it has to be notice that the accuracy of the algorithm used for extracting and matching the keypoint affect directly the result of the registrations.

intensity-based registration algorithm. This algorithm uses all the image information. For that reason with this method it is possible avoid the error in extracting and matching features. The registration algorithm based on mutual information usually has more precision and more robust result than the feature-based registration algorithm.

Despite the various application illustrated before of medical imaging registration, we are going to focus our work in lungs registration. At present, Lung diseases are probed mainly through CT technology. CT scans can form high-resolution tissue slice images, it is able to demonstrate the organizational structure of lung lesions area clearly.

Frequently in lungs image, due to the relative abundance of high-contrast, it is simple select manually the keypoint.In fact expert landmark correspondences are widely reported for evaluating deformable image registration (DIR) spatial accuracy, despite using the discuss algorithm.

Deformable image registration (DIR) has many exciting potential applications in diagnostic medical imaging and radiation oncology. However, in order to use any of this applications is important achieve a good spatial accuracy in DIR process. Nowadays, as a result of his complexity, DIR is still an open problem in the research world.

2 PROBLEM STATEMENT

In this report we will face the image registration of chest CT volumes 4DCT (four-dimensional computed tomography) DIR-Lab Challenge presented on the website 'www.dir-lab.com', that consists in the evaluation of DIR spatial accuracy using large sets of expert-determined landmark point pairs. The image of the patient's lungs are acquired in two different conditions:

- maximum inhalation phase.
- maximum exhalation phase.

The solution adopt for this problem is mainly based on elastix frame work. Furthermore different techniques of prepossessing have been applied in order to increase the accuracy of the DIR.

3 OBJECTIVE

The goal of this project is to develop a consistent framework for the objective evaluation of thoracic DIR. This framework is based on the use of large samples of expert-determined landmark feature pairs between volumetric images as a reference for spatial accuracy measurements.

4 MATERIALS

4.1 DATASET

For this project were given 4 cases of patients affected by Chronic obstructive pulmonary disease (COPD), for training purpose. Each cases had received CT imaging of the entire thorax in the supine position at normal expiration and maximum effort full inspiration. The images were given in a raw file. Each image set was reconstructed, in matlab or ITK, according to image dimensions 512 × 512 x N. The N dimension is different in each single case and it can be read from the website of the challenge. It has to be notice that the image dimensions are given in voxel units, and the voxel dimensions are given in millimeters. All the information about the images are reported in the table 4.1

Table 4.1: Dataset specifications

Label	**Image Dims**	**Voxels (mm)**	**Displacement (mm)**
COPD1	512 x 512 x 121	0.625 x 0.625 x 2.5	25.90 (11.57)
COPD2	512 x 512 x 102	0.645 x 0.645 x 2.5	21.77 (6.46)
COPD3	512 x 512 x 126	0.652 x 0.652 x 2.5	12.29 (6.39)
COPD4	512 x 512 x 126	0.590 x 0.590 x 2.5	30.90 (13.49)

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States and is projected to be the third leading cause of death worldwide by the year

2020 (Lopez 1998). The COPDgene study (www.copdgene.org) is a National Heart Lung Blood Institute (NHLBI) funded cross-sectional study, with a recruitment goal of over 10 000 patients, designed to discover what genetic factors contribute to the development of COPD. [1]
For each case was also given a txt file containing a set of landmarks points corresponding to the inhalation and exhalation phase. Moreover another 2 new cases, with only the landmark corresponding to the moving image, it has been given with the aim of evaluate the algorithm implemented.

4.2 Tools

ELASTIX For computing all the transformations, the Elastix framework has been used. Elastix is a program used for alligning/registering images. It supports different type of transformations such as: affine and B-spline. The program is mainly handled by the command terminal [2]. Large parts of the code in elastix are based on the Insight Segmentation and Registration Toolkit (ITK).

MATLAB Matlab has been used in order to compute the preprocessing of the image, and in addition we decide to use matlab to upload the raw file.

ITK-SNAP For monitorize all the transformation we have also used the tool ITK-SNAP, a software application used to visualize, segment and handle structures in 3D medical images [3].

ELASTIX FROM MATLAB is a collection of wrappers for the open source image registration suite Elastix, which allows to integrate Elastix from Matlab.

5 METHODOLOGY

5.1 Preprocessing

Preprocessing of the image has been one of the crucial part of the project. As we already explained in the section before, the data were given in a raw format. When the image were uploaded in one of the used software it was possible to see that the histogram was having a quite unusual shape. It has to be notice that is really important the choose of the format of the data. As first approach has been tried to upload the data as unsigned 16(uint16) integer, however when the histogram was visualized it was clear that unsigned integer was not the correct format, in fact was noticed that the histogram was squished around the 0 value as it is shown in the fig 5.1

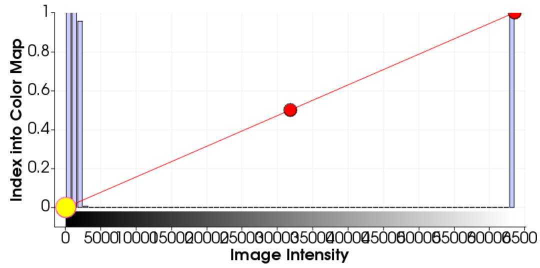


Figure 5.1: Unsigned histogram

The correct way to upload the data was the signed integer 16(int16), as it is actually suggest from the website of the challenge. The resulting histogram is shown in the fig:5.2 and the images are shown in the figure fig 5.4

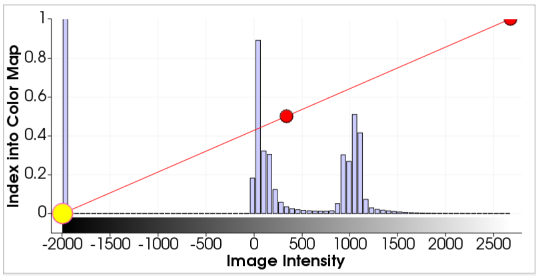


Figure 5.2: Signed histogram

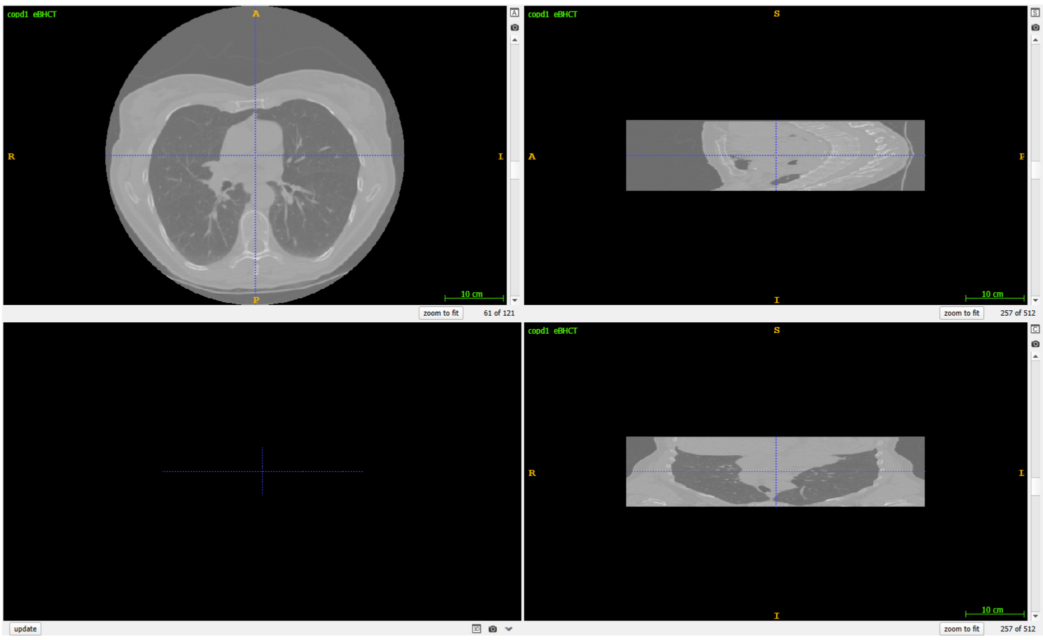


Figure 5.3: Raw image

Looking at the image it is easy to realize that there are some operations needed in order to have better quality. Regarding the data uploading process it is important to notice that other few settings can be adjusted:

1. The pixel with negative intensity value belongs to the surrounding area of the chest (gray circle fig: 5.4). In order to build a mask and to have better result in the transformation it is useful to remove this pixel. In the figure XXX is shown the images after this operation was done.

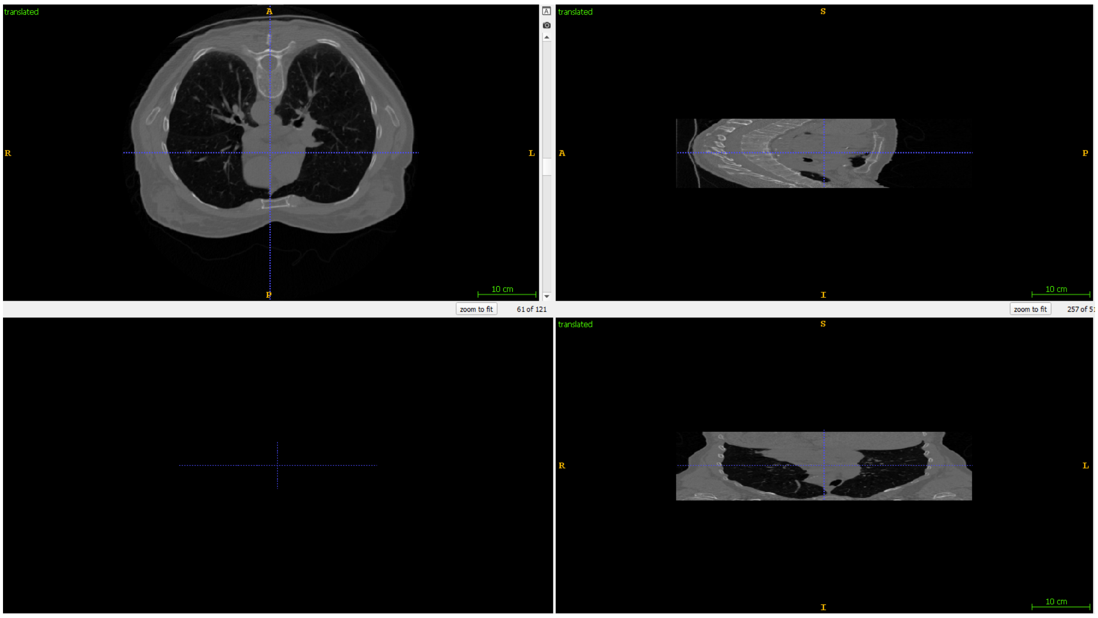


Figure 5.4: Image without negative values of the histogram

2. Image orientation has to be handled with attention, especially the z direction. The important thing in the orientation is the coherence between the 3 axis. In the image 5.4 it is possible to see that the images are upside down, however all the 3 view respect the same orientation.

3. Another parameter that needs to be set in upload phase is the voxel spacing. For each case is given the value of the voxel spacing in order to visualize the image in a correct way. However, for getting better registration result, it has been decide to work with an isotropic voxel of 2.5 mm. This value correspond to the maximum length of the original voxel spacing. Anyway during the visualiztion of the image has been necessary to go back to the suggest voxel spacing.

5.2 Mask

Different strategy has been tried during the progress of this project. One approach has consisted in masking the image, and applying the transformation only in the region of interest (ROI). The mask has been generated in matlab code starting from the raw image. Before generating the mask the negative value of the intensities were removed, after that was applied the function of matlab 'graythresh'. This function computes a global threshold 'level' that can be used to convert an intensity image to a binary image with the other matlab function imbinarize. Because of the difference in the intensity of the lungs and surrounding area the result mask was good. The mask for one image is shown in the figure 5.5

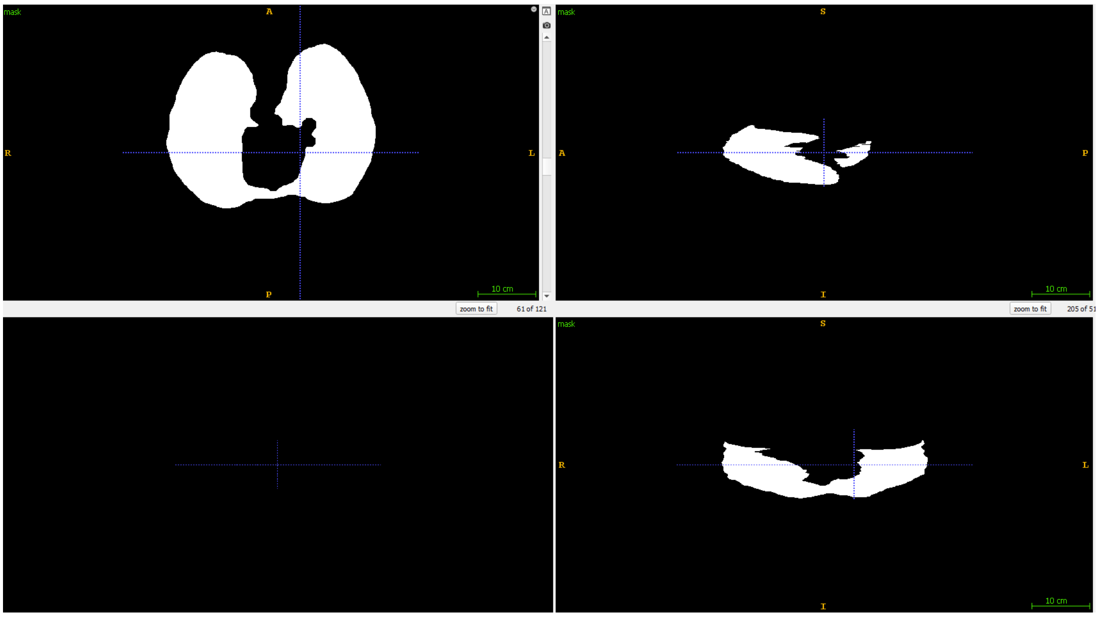


Figure 5.5: Mask

5.3 Non local means

Since the images acquired by the instrument were clearly corrupted by noise, it has been tried to apply a denoising algorithm. The algorithm applied was a non local mean algorithm, and it has been taken from the professor Vicente Manjon. However in our case no improvement in the final result registration was achieved after the denoising. On the contrary, due to the fact that some crucial structure for the registration were deleted by the algorithm, the result of the final result was worse in the denoised image.

5.4 Volumes Registration

The registration of volumes is performed in several consecutive steps starting from faster rough prealignment and further more accurate registration. As the rough prealignment stage affine transformations were performed on the images. This results in a rough alignment of the aligned shapes. Since this transformation is rigid, it doesn't deform the shape of the lungs to properly match each other, however it brings them closer by only performing rotation and scaling.
The affine transformation is performed using a multi resolution pyramid, which allows to achieve a faster computation time for the alignment process.
Afterwards, another type of transformation is performed in order to actually tackle the challenge of lung image registration. This type uses a deformable grid, that can be stretched and moved in all of the directions. It is the B-Spline transformation, that stands for basic spline and such that every spline can be defined as a set of B-Splines on a set of support points. The deformable grid can have various cell dimensions(the bigger the dimension the less precise the end transformation may become, but the faster it is computed).

The registration of images doesn't really depend on the initial orientation of the images, since with a specific set of parameters images will be even oriented before registration according to their center of gravity and primary axes, however we have to ensure that the set of landmark points that are given in order to measure the registration accuracy are oriented in the same way as the registered images. Otherwise it would be impossible to apply the transformation matrix extracted from the final result of registration on these sets of points. Thus, we have to determine which orientation of images corresponds to the given orientation of landmarks.

5.4.1 Masking

The given lung images contain data, that in theory is not necessary for the intensity based registration process, moreover it can force the algorithm to align not the important organ tissue regions, but the edges of outlier objects of the image. Thus, there is a need to extract the most important information from the image, which in our case are the two lungs themselves.
The mask generation was described above in the pre processing section. Now, the registration using the defined masks will be explained. The first approach involves applying the binary masks on the input images before the registration process. In this way all the unnecessary data is removed from the images right away, however in order to actually perform registration of the original images one would have to extract the obtained transformation matrix from the result and apply it to the original set of images where all the information is preserved.

Nevertheless, this approach has a serious drawback: while we remove the irrelevant objects from the images, in fact we create a high contrast edge between the object of interest(lungs) and the background. This means that the intensity based registration algorithm will strongly aim to align these edges rather than the organ tissue structures.

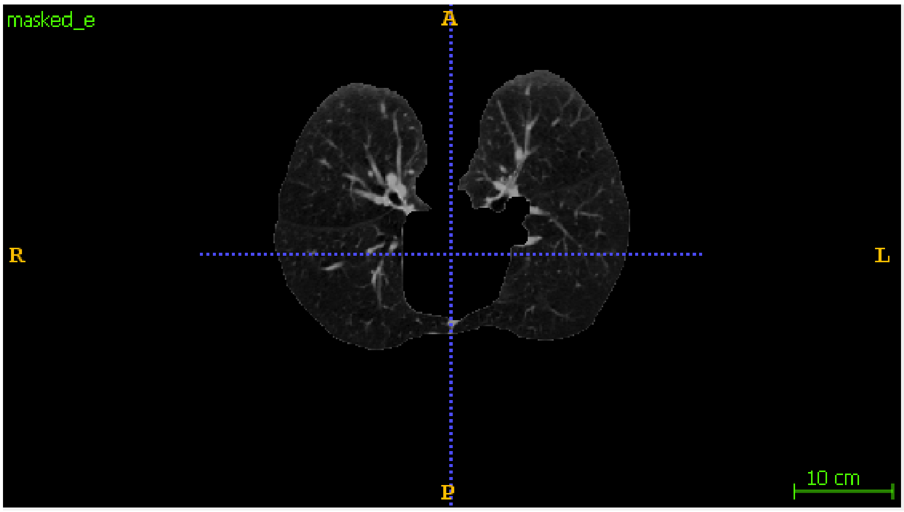


Figure 5.6: Original image after applying the extracted binary masks.

An alternative approach involves the usage of a specific feature of the Elastix registration framework. There is a possibility to only define the region of interest on the images by passing the masks to the algorithm. If one passes a mask for only the fixed image, the image sampler during every iteration of the algorithm finds 2048 samples that lay within the selected region of both images in accordance with the provided mask.

Figure 5.7: Extracted mask that is passed to the Elastix registration framework as an additional parameter.

5.5 Registration results assessment and parameter tuning

In this section the final as well as intermediate results of intensity based lung image registration will be presented.
To implement a basic registration on the images didn't take much time to develop, however a lot of time during the project was spent on finding the correspondences between the orientation and meta data of the images and the landmark points used for the result evaluation. Finally it was discovered that in order to find a transformation that can later directly be performed on the set of points, it is required to have the RPS orientation set on all pairs of images, and that the transformation has to be performed by passing the indexes of the pixels, but not the physical voxel coordinates to $transformix$ command of $elastix$.

There is also a possibility to give different meta data to the input images such as voxel spacing. The default voxel spacing for the given dataset is not isotropic(e.g. 0.625, 0.625, 2.5), which means that the transformations among different axes actually have different weights with respect to their physical transformation effect. At first the tests were performed on this initial configuration of voxel spacing. The results have proven to be rather unsatisfying. The registration error actually didn't improve significantly or even became larger after running the algorithm.

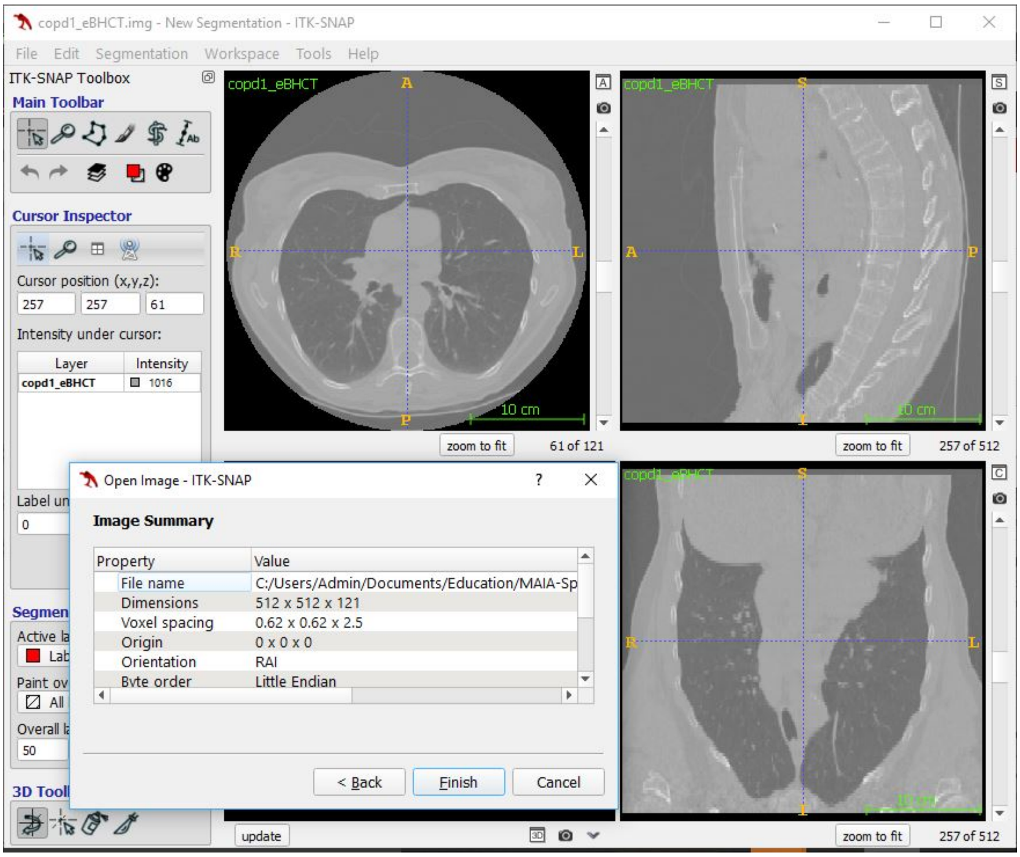


Figure 5.8: Exhaled image visualization for pair 1 with original non isotropic voxel spacing (0.625, 0.625, 2.5)

Therefore, it was decided to test the algorithm with an isotropic spacing, thus it was chosen to be $(1,1,1)$, where spacing is equal among all axes, where each pixel size is 1 cubic millimeter. This configuration slightly improved the result however we have noticed that the acquired error is the biggest among the z ordinate axis and we realized that we probably should preserve the initial spacing on this axis, but still keep the coordinate system isotropic. In this way, we have chosen the spacing to be $(2.5, 2.5, 2.5)$, where the two first dimensions are stretched to be of 2.5mm each, and the z ordinate is preserved. Interestingly, this change has introduced a significant improvement on the final registration error. Thus, the error dropped from 9.83 to 6.13 for the first image pair.

Figure 5.9: Exhaled image visualization for pair 1 with isotropic voxel spacing (2.5, 2.5, 2.5)

Later improvements were introduced by optimizing the parameters of the transformation. We have tried multiple parameter sets. We have discovered a database that describes optimal registration settings according to the image modalities. After multiple experiments, it was decided to choose the following configuration for consecutive Affine and B-Spline transformations.

```
//ImageTypes
(FixedInternalImagePixelType "float")
(FixedImageDimension 3)
(MovingInternalImagePixelType "float")
(MovingImageDimension 3)
(Origin 0.0000000000 0.0000000000 0.0000000000)
(Spacing 2.5000000000 2.500000000 2.500000000)

//Components
(Registration "MultiResolutionRegistration")
(FixedImagePyramid "FixedSmoothingImagePyramid")
(MovingImagePyramid "MovingSmoothingImagePyramid")
(Interpolator "BSplineInterpolator")
(Metric "AdvancedMattesMutualInformation")
(Optimizer "StandardGradientDescent")
(ResampleInterpolator "FinalBSplineInterpolator")
```

```
(Resampler "DefaultResampler")
(Transform "AffineTransform")

// ********** Pyramid

// Total number of resolutions
(NumberOfResolutions 4)


// ********** Transform

(AutomaticTransformInitialization "true")
(AutomaticScalesEstimation "true")
(HowToCombineTransforms "Compose")


// ********** Optimizer

// Maximum number of iterations in each resolution level:
(MaximumNumberOfIterations 1000)

//SP: Param_a in each resolution level. a_k = a/(A+k+1)^alpha
(SP_a 500.0)

//SP: Param_alpha in each resolution level. a_k = a/(A+k+1)^alpha
(SP_alpha 0.602)

//SP: Param_A in each resolution level. a_k = a/(A+k+1)^alpha
(SP_A 50.0)


// ********** Metric

//Number of grey level bins in each resolution level:
(NumberOfHistogramBins 32)
(FixedLimitRangeRatio 0.0)
(MovingLimitRangeRatio 0.0)
(FixedKernelBSplineOrder 1)
(MovingKernelBSplineOrder 3)


// ********** Several
(WriteTransformParametersEachIteration "false")
(WriteTransformParametersEachResolution "false")
(WriteResultImage "false")
(ShowExactMetricValue "false")
//(ErodeFixedMask "false")
//(ErodeMovingMask "false")
(ErodeMask "false")
(UseDifferentiableOverlap "false")

```

```

// ********** ImageSampler

//Number of spatial samples used to compute the mutual information in each resolution
    level:

(ImageSampler "Random")
(NumberOfSpatialSamples 2048)
(NewSamplesEveryIteration "true")




// ********** Interpolator and Resampler

//Order of B-Spline interpolation used in each resolution level:
(BSplineInterpolationOrder 1)

//Order of B-Spline interpolation used for applying the final deformation:
(FinalBSplineInterpolationOrder 3)

//Default pixel value for pixels that come from outside the picture:
(DefaultPixelValue 0)
```

And for the B-Spline transformation:

```
// ********** Image Types

(FixedInternalImagePixelType "float")
(FixedImageDimension 3)
(MovingInternalImagePixelType "float")
(MovingImageDimension 3)


// ********** Components

(Registration "MultiResolutionRegistration")
(FixedImagePyramid "FixedSmoothingImagePyramid")
(MovingImagePyramid "MovingSmoothingImagePyramid")
(Interpolator "BSplineInterpolator")
(Metric "AdvancedMattesMutualInformation")
//(Metric "AdvancedMeanSquares")
(Optimizer "StandardGradientDescent")
(ResampleInterpolator "FinalBSplineInterpolator")
(Resampler "DefaultResampler")
(Transform "BSplineTransform")


// ********** Pyramid

// Total number of resolutions
(NumberOfResolutions 4)
```

```
// default schedule: isotropic upsampling with factor 2

// ********** Transform

(FinalGridSpacingInPhysicalUnits 12.0 12.0 12.0)
(GridSpacingSchedule 1.0 1.0 1.0 1.0)
(HowToCombineTransforms "Compose")


// ********** Optimizer

// Maximum number of iterations in each resolution level:
(MaximumNumberOfIterations 1000)

//SP: Param_a in each resolution level. a_k = a/(A+k+1)^alpha
(SP_a 10000.0)

//SP: Param_alpha in each resolution level. a_k = a/(A+k+1)^alpha
(SP_alpha 0.602)

//SP: Param_A in each resolution level. a_k = a/(A+k+1)^alpha
(SP_A 50.0)


// ********** Metric

//Number of grey level bins in each resolution level:
(NumberOfHistogramBins 32)
(FixedLimitRangeRatio 0.0)
(MovingLimitRangeRatio 0.0)
(FixedKernelBSplineOrder 1)
(MovingKernelBSplineOrder 3)


// ********** Several

(WriteTransformParametersEachIteration "false")
(WriteTransformParametersEachResolution "true")
(WriteResultImageAfterEachResolution "false")
(WriteResultImage "true")
(ShowExactMetricValue "false")
(ErodeMask "false")


// ********** ImageSampler

//Number of spatial samples used to compute the mutual information in each resolution
    level:
(ImageSampler "Random")
(NumberOfSpatialSamples 2000)
(NewSamplesEveryIteration "true")
```

```
(UseRandomSampleRegion "false")


// ********** Interpolator and Resampler

//Order of B-Spline interpolation used in each resolution level:
(BSplineInterpolationOrder 1)

//Order of B-Spline interpolation used for applying the final deformation:
(FinalBSplineInterpolationOrder 3)

//Default pixel value for pixels that come from outside the picture:
(DefaultPixelValue 0)
```

As an image sampler random sampler has been chosen. It randomly selects a user-specified number of voxels from the fixed image and every voxel has equal chance to be selected. The Grid image sampler, that should grant better reproducibility of the results because of it's fixed and not randomized selection way, has in fact proven to increase the final registration error slightly.

We have chosen the optimizer function to be the StandardGradientDescent that is more accurate than Robbins-Monro optimizer and computation time is not as important as the final result accuracy in our case. The parameters for stochastic gradient descent where chosen according to the Elastix Database (http://elastix.bigr.nl/wiki/index.php/Parameter$_{f}ile_{d}atabase$). Other parameters are chosen according to the modality type of the processed images.

5.6 Project Management

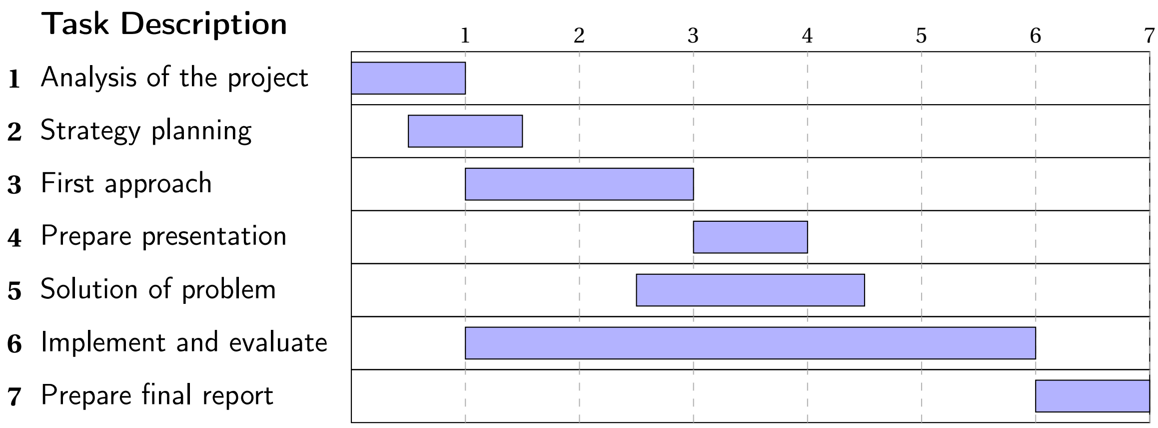


Figure 5.10: Project Management Part A

6 RESULTS

After various experiments with the preprocessing, masking and registration algorithm configurations, the best approach was selected. This involves registering the images without the application of masks, neither using the non-local means denoising algorithm. The obtained result was improved to be as shown by choosing the most suitable registration framework configuration.

Images	Initial error (mm)	Error registered (mm)	Error registered preprocessed (mm)
Pair 1	26.33 ± 11.44	4.57 ± 3.77	!
Pair 2	21.78 ± 6.47	9.98 ± 7.28	!
Pair 3	12.63 ± 6.40	9.78 ± 6.57	!
Pair 4	29.58 ± 12.94	11.97 ± 7.58	!

Figure 6.1: Initial and final registration results for the 4 given image pairs.

The last column of the table is not presented since all of the presented preprocessing techniques resulted in a greater registration error. The main error behaviour was presented above in accordance with the proposed approaches.

7 CONCLUSIONS

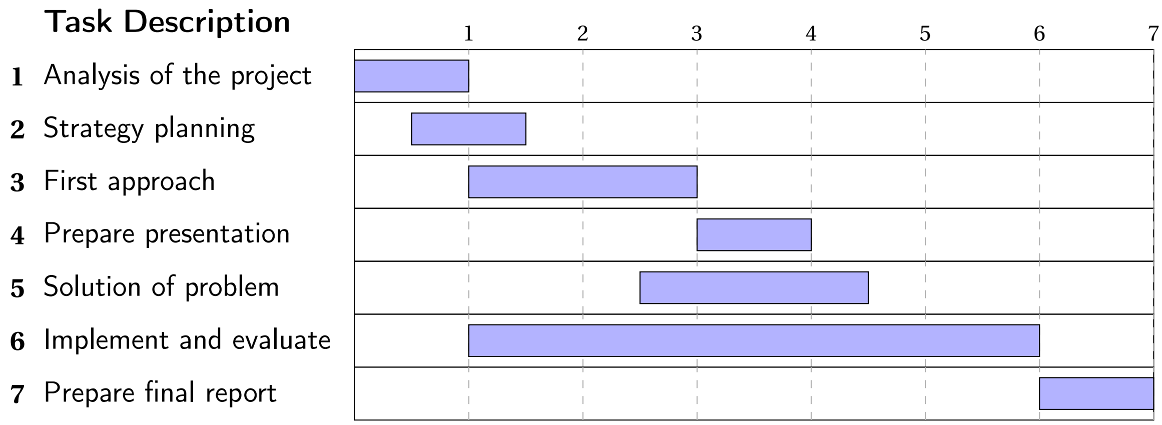
During this project quite a few approaches were tested: image denoising using non-local means algorithm, ROI detection by lung mask extraction, contrast enhancement, voxel space modification, registration framework parameter tuning, etc. However not all of the techniques have improved the quality of registration.

Denoising, in fact, ruined some important details, and thus it deteriorated the result. Image masking also didn't bring any improvement.

The biggest change that was introduced was due to the optimal configuration of the registration framework.

As a possible way of improvement, it was planned to use a multiresolution B-Spline Grid, that would theoretically enhance the computation time, without any drawback on the accuracy.

8 PROJECT MANAGEMENT



References

[1] Richard Castillo et al. “A reference dataset for deformable image registration spatial accuracy evaluation using the COPDgene study archive”. In: *Physics in medicine and biology* 58.9 (2013), p. 2861.

[2] Stefan Klein et al. “Elastix: a toolbox for intensity-based medical image registration”. In: *IEEE transactions on medical imaging* 29.1 (2010), pp. 196–205.

[3] Paul A. Yushkevich et al. “User-Guided 3D Active Contour Segmentation of Anatomical Structures: Significantly Improved Efficiency and Reliability”. In: *Neuroimage* 31.3 (2006), pp. 1116–1128.