

Atlas-based segmentation of the bladder and rectum in prostate cancer patients: Application to radiotherapy

Dissertation presented by
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Abstract

Nowadays, more than half of the patients suffering from cancer will need radiotherapy during their treatment. Radiotherapy is a treatment modality that uses radiation to irradiate cancerous cells to destroy them by blocking their ability to proliferate. Unfortunately, these radiations will also reach healthy cells. In order to spare the healthy tissues while maximizing the dose in the tumor a plan has to be established before the treatment. This plan requires a precise segmentation of the tumor and of the organs around it. Currently this delineation step is manually executed by physicians at the hospital and is very time consuming. Moreover a radiotherapy treatment consists of approximately 30 sessions spread over 5-6 weeks. During this period, patients may undergo anatomical changes due to weight loss or due to the treatment. The plan should potentially be adapted to take these changes into account, requiring a new delineation step to spot these changes and determine the new plan. In this context, we evaluate in this master thesis several methods that use atlases and pairwise registration in order to automatically segment the bladder and the rectum in prostate cancer patient on CT and CBCT images. The goal being at first to give indications to the physicians about the need for re-planning or not and then to be used as an actual contour during the planning.

Contents

Contents	ii
List of figures	v
List of abbreviations	vii
Acknowledgment	ix
1 Introduction	1
1.1 Medical context	1
1.2 Radiotherapy	1
1.2.1 Clinical workflow	4
1.3 Challenges and objectives	8
1.4 Organization of the document	9
2 Image registration	11
2.1 Transforms	12
2.2 Interpolators	13
2.3 Metrics	14
2.4 Optimizers	16
2.5 Image samplers	16
2.6 Multi-resolution	17
2.7 Summary	17
3 State of the art	19
3.1 Use of image registration in radiotherapy	19
3.2 Methods for automatic segmentation	20
3.3 Summary	25
4 Segmentation using atlas-based registration	27
4.1 Materials	27
4.2 Methods	30

4.2.1	Registration	31
4.2.2	Atlas selection	33
4.2.3	Label fusion	34
4.3	Results and discussion	35
4.4	Robustness to CBCT	49
4.5	Source of errors in registration	54
4.6	Summary	56
5	Conclusion	57
A	Image used as atlas and target image	65

List of figures

1.1	Linear dose distribution according to depth	2
1.2	Beam arrangement and dose distribution: example	3
1.3	Clinical workflow of radiotherapy.	4
1.4	Example of DVH for prostate cancer	6
1.5	Impact of anatomical changes on the dose distribution	7
2.1	Basic mechanics of image registration	12
2.2	Kind of transformations	13
2.3	Illustration of interpolation.	14
2.4	Example of iterative optimization for a translation	16
3.1	Different methods for atlas based segmentation	22
4.1	Example of 3D view of a patient on slicer 3D.	28
4.2	Anatomical structure in the pelvic region	28
4.3	Example of changes in the grey level between patients.	29
4.4	Multi-atlas segmentation method.	31
4.5	Example of a slice of a patient and his associated atlas.	32
4.6	Comparison of SSD metric and MI metric.	36
4.7	The interesting part of the 3D image.	37
4.8	Boxplot of the DSC for the ten query images.	38
4.9	Comparison of different ranking methods.	39
4.10	Visual comparison of different methods on transverse slices.	41
4.11	Visual comparison of different methods on coronal slices.	42
4.12	Visual comparison of different methods on sagittal slices.	43
4.13	Visual comparison of different methods for the rectum.	44
4.14	Comparison with selection of the best atlases.	45
4.15	Comparison of different fusion methods for the bladder.	46
4.16	Comparison of different fusion methods for the rectum.	47
4.17	Step by step example of thresholding and morphological operation.	48
4.18	Comparison of atlas based method and thresholding method.	48

4.19	Visual comparison of thresholding and atlas-based method . .	49
4.20	Comparison between CT and simulated CBCT.	50
4.21	Comparison of different ranking methods in CBCT.	52
4.22	Comparison of the DSC on CT and on CBCT.	53
4.23	Visual comparison of our method on CT and CBCT.	54
4.24	Example of error sources in registration.	55
A.1	Patient 1.	65
A.2	Patient 2.	65
A.3	Patient 3.	66
A.4	Patient 4.	66
A.5	Patient 5.	66
A.6	Patient 6.	67
A.7	Patient 7.	67
A.8	Patient 8.	67
A.9	Patient 9.	68
A.10	Patient 10.	68
A.11	Patient 11.	68
A.12	Patient 12.	69
A.13	Patient 13.	69
A.14	Patient 14.	69
A.15	Patient 15.	70
A.16	Patient 16.	70
A.17	Patient 17.	70
A.18	Patient 18.	71
A.19	Patient 19.	71
A.20	Patient 20.	71

List of abbreviations

ART: Adaptive radiation therapy
CBCT: Cone beam computed tomography
CC: Cross correlation
CT: Computed tomography
DSC: Dice similarity coefficient
DVH: Dose volume histogram
IGRT: Image-guided radiotherapy
MI: Mutual information
MRI: Magnetic Resonance Imaging
MSD: Mean squared difference
NCC: Normalized correlation coefficient
NMI: Normalized mutual information
OAR: Organ at risk
PET: Positron Emission Tomography
RT: Radiotherapy
SSD: Sum of squared difference

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Chapter 1

Introduction

1.1 Medical context

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [1]. In 2012, there were 14 million new cases of cancer and approximately 8 million people were killed by this disease during the year 2015 worldwide. That makes it one of the leading reasons of death with one in six deaths due to cancer [2]. Moreover, it is estimated that these numbers can only increase due to demographic growth, aging, and frequency increase. By 2030 we could have annually 26 million new cases and 17 million deaths [3].

In this context, it is more and more important to enhance the methods that can heal cancer or at least improve the living conditions or increase the time lifetime of a patient. It can among others be cured thanks to surgery, chemotherapy or radiotherapy. Moreover, it has been shown that the proportion of cancers where radiotherapy is indicated was approximately 50% [4]. These are the reasons why it is interesting nowadays to work on methods that can improve this technology.

1.2 Radiotherapy

As explained before, radiotherapy is one of the leading methods to cure cancer or improve life of cancer patients. It relies on the fact that when a cell is exposed to radiation, it can be killed by these radiations. Indeed, radiations damage the genetic material of the cell (DNA) causing single or double strands break. These damages will block the ability of the cell to divide and proliferate [5].

Unfortunately, when we irradiate the tumor we also damage the surrounding healthy tissues. This irradiation depends on the kind of radiation that we use to treat the patient. Indeed, as we can see in Figure 1.1 there is a difference between the conventional radiotherapy that uses photons to treat the patient and proton therapy that uses protons. X-ray photons, used in conventional radiotherapy, deposit their energy all along their path and thus there is some dose deposit before and after the tumor. On the other hand, protons, used in proton therapy, are heavy charged particles and do not have the same behavior as x-ray while traveling through matter. A proton loses most of his energy at the end of his path in what we call the Bragg peak. This peak is visible on the left of Figure 1.1. The goal of proton therapy is to align the Bragg peak with the tumor in order to deposit a maximum of dose in the tumor and a minimum of dose in the healthy tissues. In reality we use protons of different energies and thus with different Bragg peaks in order to treat all the tumor. The addition of these peaks will give a broader peak that will encompass the tumor. This spread out Bragg peak is visible in blue dotted line on Figure 1.1. Due to those properties, we see in orange in Figure 1.1 that photons deposit more dose in healthy tissues than protons.

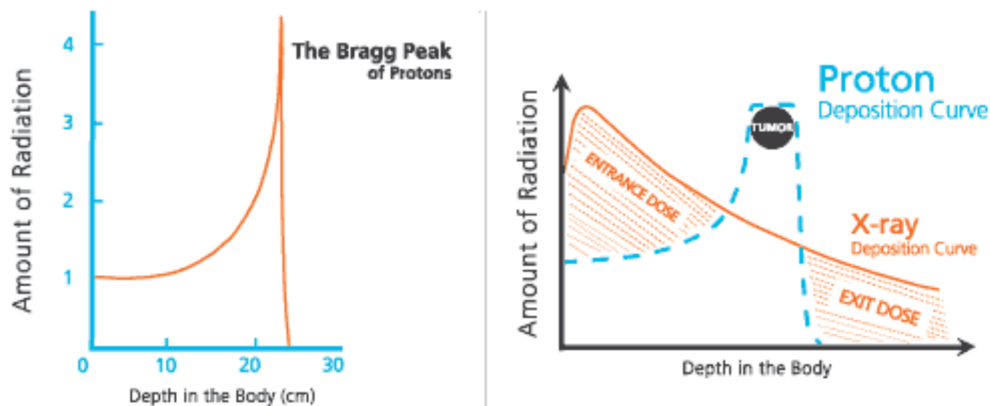


Figure 1.1: The left image represents the Bragg peak of a proton. In the right image, we compare the dose deposit of x-ray and protons ¹.

¹https://www.floridaproton.org/what-is-proton-therapy/terms?utm_content=buffera0cc&utm_medium=social&utm_source=linkedin.com&utm_campaign=buffer. accessed February 18, 2018.

Nevertheless, there are actually few randomized controlled trials in order to prove that proton therapy is always better than radiotherapy [6]. Moreover a proton therapy session is more expensive than a conventional radiotherapy treatment. Indeed the cost is approximately 1000 euros for one session of proton therapy while it costs around 200 euros for conventional treatment [7].

Physicians and medical physicists modulate the intensity of the beam according to the direction in which it arrives on the tumor in order to have an accumulation of dose in the tumor higher than in the surrounding tissues. We call that dose sculpting. An example can be seen on Figure 1.2. In this Figure we can see that the tumor is exposed to radiation in three different directions thanks to a rotating gantry that is able to rotate all around the patient. The yellow arrows represent the intensity of the beam and this intensity is not the same everywhere. Indeed the tumor can have a lot of different shapes and we will use a collimator at the exit of the gantry in order to attenuate the energy of the beam in some location so that the energy deposit optimally fits the tumor contour.

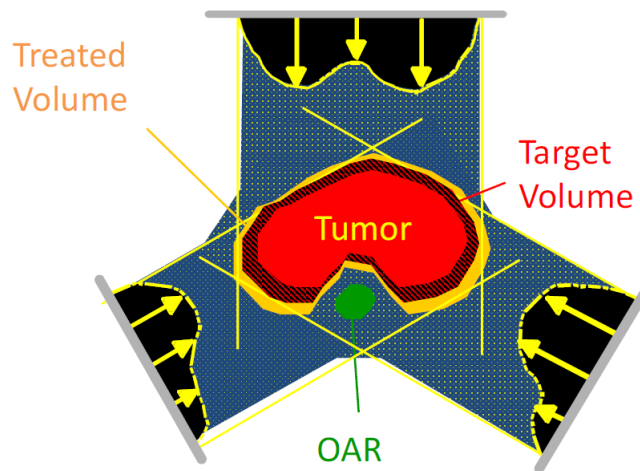


Figure 1.2: Beam arrangement and dose distribution: example. The beam is modulated thanks to collimator and rotating gantry in order to have a dose distribution that fits the contour of the tumor and spares the organ at risk (OAR). The yellow arrows represent the intensity of the beam. Finally the target volume is a bit greater than the tumor because of the margins that we use during the planning ¹.

¹Course LGBIO2070: Engineering challenges in protontherapy

Moreover, it is known that DNA of cancerous cells repair more slowly and produce more DNA breaks than normal cells [5]. Thus a radiotherapy treatment consists of irradiation of the tumor (and therefore its surrounding tissues) several times for several weeks in order maximizes the effect of radiation on cancerous cells and minimizes the negative side effects on healthy cells. This is what we call the dose fractionation.

1.2.1 Clinical workflow

As we have seen before, the goal of radiotherapy is to kill unhealthy cells by irradiation while avoiding the healthy cells. For this reason it is important to know in advance precisely where the tumor is located and what are the organs that we have to avoid in its vicinity. We also have to calculate how much dose each part will receive according to a plan. A plan describes how the radiation dose is delivered to the patient. That's the reason why there are mandatory preparatory steps before actual treatment.

A typical workflow is visible on Figure 1.3 and will be explained below.

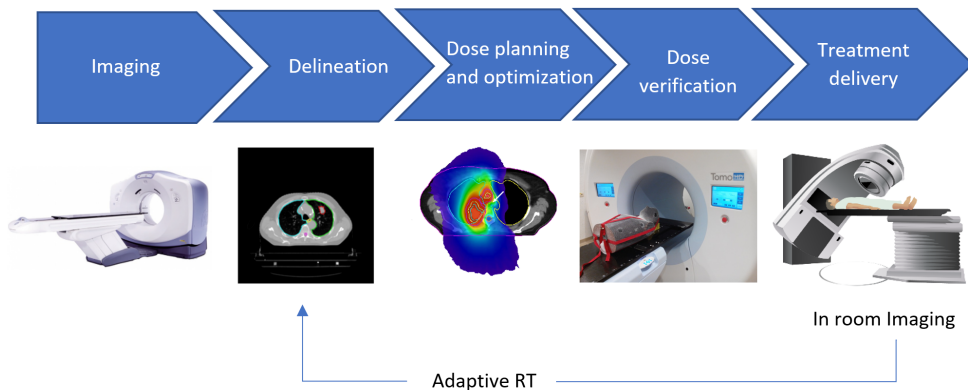


Figure 1.3: Clinical workflow of radiotherapy.

The first step is the imaging step. During this step we will acquire 3D anatomical images of the patient. These images are acquired in a CT Scan and will give X-ray images of slice of the patient that we can aggregate in order to have a 3D image.

In the delineation step, the physician delimits the contour of each organ and tumor on the image acquired previously.

In the third step, the physician evaluates the dose that the tumor must receive and the number of fractions needed. Then there is an optimization phase where the physicist tries to find the best plan in order to have a maximum of dose in the tumor and a minimum in the OAR conform to the prescription.

While the best plan is estimated, the doctor checks if the plan is in accordance with the requirements and validates it or not.

Finally the treatment is administered to the patient in several fractions. The patient comes to the hospital more or less 5 days a week for 5 to 8 weeks to receive the treatment [8]. Each time the patient comes in the treatment room, he must be aligned so that the simulation geometry can be reproduced in the treatment room. One of the possible methods is to use marks on the patient and lasers [9]. Another method consists in using in room imaging in order to align the images taken in the room with the images used for planning. Such images can be obtained thanks to cone-beam computed tomography (CBCT). The CBCT is an in room imaging system that is integrated in the treatment device.

1.2.1.1 Organ and tumor delimitation

One of the steps described before is the delineation of the tumor and OARs. An error during this step can negatively impact the computation of the dose distribution and thus the patient treatment. Indeed, in proton therapy the energy loss by the radiation will change depending on the type of tissues that the radiation will cross. So, it is important to know where we will find which kind of tissues. Moreover, with a wrong delimitation of the tumor or of the organs, there is a high risk to give a higher dose to organs that may be considered as organs at risk (OAR). A wrong irradiation could have a dramatic impact. Indeed, if we irradiate healthy cells they can become cancerous cells and thus lead to new cancer.

Another important reason to have the delineation of each organ is to compute the dose volume histogram (DVH). A DVH is a histogram relating radiation dose (in Gray) to tissue volume. They are mostly used to evaluate different plans during the planning. An example of DVH can be seen in Figure 1.4. A good DVH is a DVH where 100% of the volume of the tumor takes a maximum of dose while a minimum of the volume of the OARs takes dose. So the curves for the OAR must be a maximum down left while the curve for the tumor must be a maximum up right.

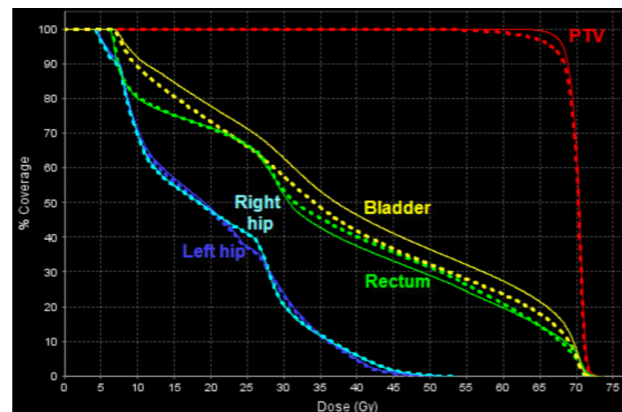


Figure 1.4: Example of DVH for prostate cancer ².

1.2.1.2 Adaptive radiotherapy

One of the problem in radiotherapy are the anatomical changes that can occur during the treatment. Indeed, during the 5-8 weeks of treatment a patient may undergo anatomical changes due to weight loss and the OARs may move a little bit. The same is true for the tumor that will also shrink due to the treatment. It is thus important to check if the dose distribution is still focused on the tumor and spares the OARs. We can see on Figure 1.5 an example of catastrophic impact due to anatomical changes in a proton therapy treatment.

²<https://www.omicsonline.org/articles-images/2155-9619-S3-e001-g004.html>, accessed May 18, 2018

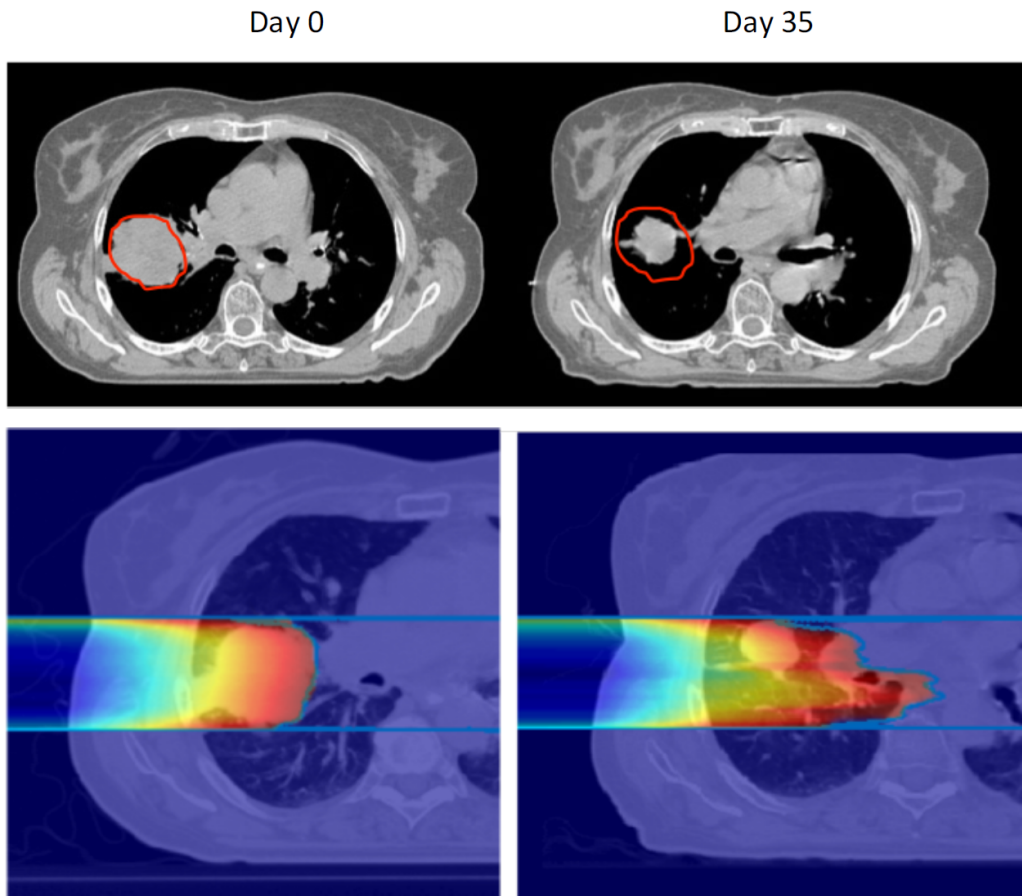


Figure 1.5: Impact of anatomical change on the dose distribution ³. In the above images we can see the contour of the tumor in red. After 35 days the tumor is not the same as at day 0. Below, we can see to the left the dose distribution (red indicates high doses) during the first day of treatment, it seems to fit quite well the tumor contour. To the right we can see the same treatment applied at day 35 after anatomical changes took place. This time the proton will deposit their energy far behind the tumor.

One of the solution to this problem is adaptive radiotherapy (ART). ART was introduced in [10] by Di Yan and is defined as a closed-loop radiation treatment process where the treatment plan can be modified using a systematic feedback of measurements. The goal of ART is to estimate the dose received by the patient after each fraction and to make a re-planning if the dose distribution is no longer true to the original plan.

³Course LGBIO2070: Engineering challenges in protontherapy.

In order to have the information about the anatomical changes we use the daily CBCT. It has the advantage of having the same iso-center as the treatment device so no patient repositioning is required. CBCT images have lower quality than conventional CT images but the use of CT requires patient transport and repositioning so it implies losses in time and accuracy. Nevertheless, efforts are made in order to integrate CT in the treatment room.

The re-planning process is done in three main steps [11]:

1. The plan is simulated from the CBCT image to calculate the actual delivered dose.
2. Structures of interest are delineated to obtain the dose volume histogram (DVH). According to this DVH the doctor can see if the plan is still effective or not.
3. If needed, the dose is recalculated in order to meet the constraints of the initial plan or to improve plan quality.

For this master thesis, we will work on the automation of second point. Indeed the process of manually contouring tumor and surrounding OARs is a long step that takes hours [11]. Knowing that a patient will come five times a week during five to eight weeks this process can be done several times for only one patient. We can understand that this task can become very time consuming regarding the number of patients who follow radiotherapy treatment. Moreover, this task is complex for both physicians and algorithms due to the low quality of CBCT images, especially for soft tissues.

1.3 Challenges and objectives

Currently the segmentation of the tumor and organs is made by hand by the physician [12]. The goal of this thesis is to use atlases (images that already have their contours) and registration methods that will align images in order to automatically segment an image of a new patient. This method will be explained later in this master thesis. In a first step the result of this automatic segmentation aims to give to the physicians indications whether a replanning is necessary or if the plan still fits the indication. In a second step it can serve as actual segmentation for the plan calculation.

One of the challenges of this master thesis is to apply this method in the pelvic region where there is a large variability inter and intra patient. Indeed,

in this region we are in the presence of organs such as the bladder and the rectum, that are organs that can vary in size and shape during the treatment but there are also lot of differences between patients. These variations can for example be due to the filling of the bladder or rectum [13].

1.4 Organization of the document

This document is divided in three parts. In chapter 2 we will make a short introduction to image registration, the main technique used in this thesis. In chapter 3 we will explain how image registration is used in radiotherapy and which methods already exist to automate segmentation of the OAR and tumor. Finally, in chapter 4 we will explain the method that we have implemented and show the result that we obtained.

Chapter 2

Image registration

As we have seen before, the delineation of organs and tumor is a very important and time consuming step. For these reasons we would like to automate this step. One of the methods used to make automatic segmentation is the use of atlas and image registration. This is why we will make a short introduction to image registration before going further on this master thesis. All the parameters that we discuss in this chapter are available on Elastix [14], the registration tool that we used in this master thesis.

The goal of images registration is to find a match between two images and to apply a geometric transform to go from an image to another. It is the task of finding a spatial one-to-one mapping from voxels in one image to voxels in the other images [15].

In order to do that we will consider images as functions that give to each voxel at coordinate $\mathbf{x}$ (x, y, z) a certain value that represents the color or the grey-value of this voxel.

We have a fixed image $I_F(\mathbf{x})$ and a moving image $I_M(\mathbf{x})$. The moving image is deformed to fit the fixed image. The goal is to find a transformation $T(\mathbf{x}) = \mathbf{x} + u(\mathbf{x})$ so that $I_M(T(\mathbf{x}))$ is aligned with $I_F(\mathbf{x})$. Note that the transformation represents the mapping of points in the fixed image to points in the moving image.

In order to have the best possible registration, we will follow a simple mechanics as the one shown in Figure 2.1. Both images are compared thanks to a metric, we then try to transform the moving image by minimizing the difference between the two images thanks to an optimizer. Then the transformation is applied to the moving image and an interpolator is used to compute

the intensity value at the mapped position. We repeat these steps until a chosen stopping criterion is met. All these steps are explained in details in sections 2.1 to 2.4. In sections 2.5 and 2.6 we will talk about methods to decrease time and calculation complexity.

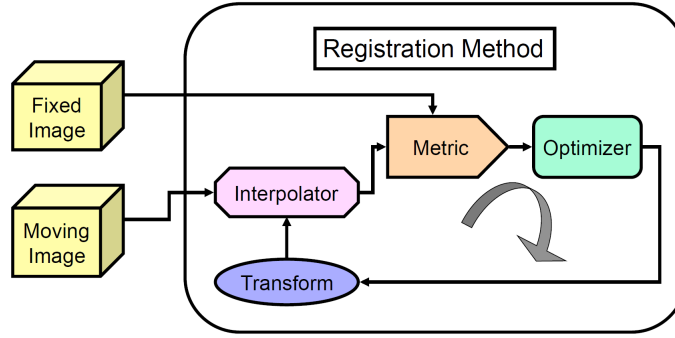


Figure 2.1: Basic mechanics of image registration ¹.

2.1 Transforms

They are different kinds of transforms. The easiest one consists simply in a translation of the image. We will then have transforms such as rigid transform that combine translation and rotation. The last linear transform that we will use is the affine transform that combine translation, rotation, scaling and shearing. All these transformations can be visualized on Figure 2.2

In addition to rigid transformations, there is non-rigid transformations such as B-splines transformations.

The mathematical definition of these transformations are:

- Translation : $T_{\boldsymbol{\mu}}(\mathbf{x}) = \mathbf{x} + \mathbf{t}$ where $\mathbf{t}$ is the translation vector and $\boldsymbol{\mu} = \mathbf{t}$.
- Rigid: $T_{\boldsymbol{\mu}}(\mathbf{x}) = \mathbf{R}(\mathbf{x} - \mathbf{c}) + \mathbf{t} + \mathbf{c}$ where $\mathbf{R}$ is a rotation matrix, $\mathbf{c}$ the center of rotation, $\mathbf{t}$ the translation and $\boldsymbol{\mu} = (\theta_x, \theta_y, \theta_z, t_x, t_y, t_z)^T$.
- Affine: $T_{\boldsymbol{\mu}}(\mathbf{x}) = \mathbf{A}(\mathbf{x} - \mathbf{c}) + \mathbf{t} + \mathbf{c}$ where the matrix $\mathbf{A}$ has no restriction and $\boldsymbol{\mu} = (a_{11}, a_{12}, a_{21}, a_{22}, t_x, t_y)^T$ in 2D.

¹LGBIO2050: Medical Imaging. Image registration

- B-splines: $T_{\boldsymbol{\mu}}(\mathbf{x}) = \mathbf{x} + \sum_{\mathbf{x}_k} \mathbf{p}_k \beta^3\left(\frac{\mathbf{x}-\mathbf{x}_k}{\sigma}\right)$ with $\mathbf{x}_k$ the control point, β^3 the cubic multidimensional B-spline polynomial, $\mathbf{p}_k$ the B-spline coefficient vector and $\boldsymbol{\mu}$ depends on the number of control points and the dimensions (2D or 3D).

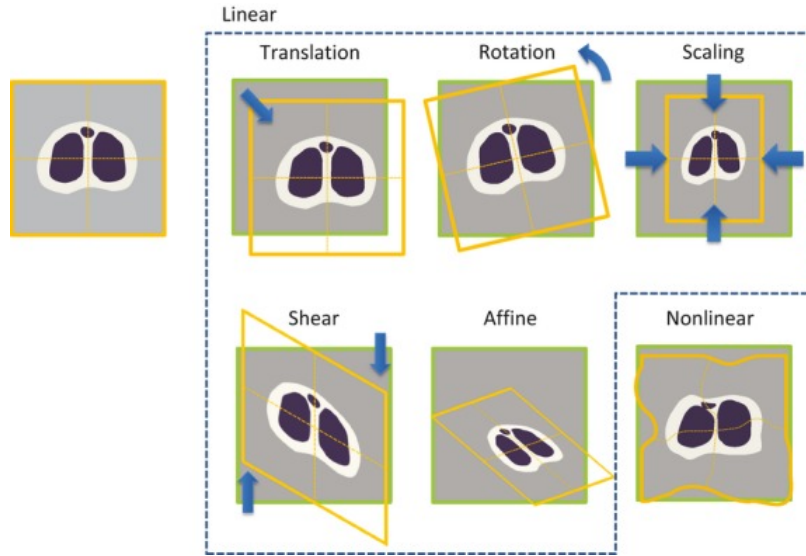


Figure 2.2: Kind of transformations ².

2.2 Interpolators

When a point is mapped from one image space to another, it will likely be mapped elsewhere than right onto voxel position. This phenomena is visible on Figure 2.3. This is the reason why we need interpolators in order to compute the intensity value at the mapped position. There are different kinds of interpolators:

- Nearest neighbor: the intensity of the nearest voxel is chosen. The same method exists with the k-nearest neighbor.
- Linear interpolator: the intensity will be the weighted average of the surrounding voxel.

²https://www.researchgate.net/figure/236125496_fig11_Geometric-transformation-functions-for-image-registration-Note-that-affine, accessed November 29, 2017.

- N-th order B-spline: the interpolant is a type of piecewise polynomial called spline. The zero-order B-spline corresponds to the nearest neighbor method and the first-order method corresponds to linear interpolation.

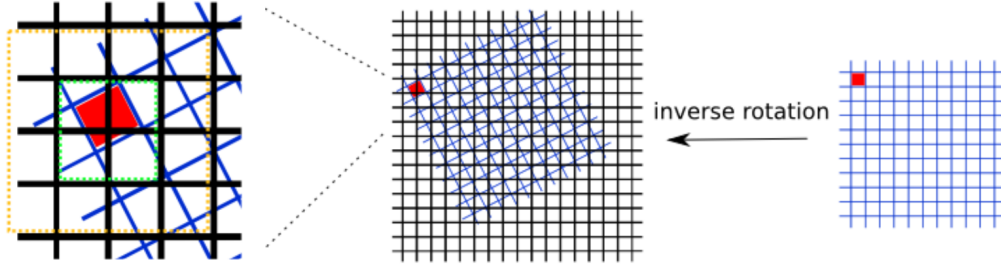


Figure 2.3: After transformation, a pixel of an image is wrongly mapped with the referential of another image.

2.3 Metrics

The metric is really important in the registration method: indeed its role is to define the similarity between the two images. The goal of the registration is to find the best parameters of the transformation in order to minimize the value of the metric. It can be written as

$$\hat{\boldsymbol{\mu}} = \operatorname{argmin}_{\boldsymbol{\mu}} C(\boldsymbol{\mu}, I_F, I_M) \quad (2.1)$$

where C is the value of the metric and $\boldsymbol{\mu}$ the parameters of the transformation. We will briefly explain below some metrics:

- Mean squared difference (MSD): it measures the average squared intensity difference between the fixed image and the moving image after transformation:

$$MSD = \frac{1}{N} \sum_i (I_F(x_i) - I_M(T_{\boldsymbol{\mu}}(x_i)))^2$$

Where $I_M(T_{\boldsymbol{\mu}}(x_i))$ denotes the image after a transformation with parameters $\boldsymbol{\mu}$ and $\sum_i$ denotes the sum over all voxels in the fixed image.

- Normalized correlation coefficient (NCC): it will measure the similarity between the two images. The goal is to maximize the function:

$$NCC = \frac{\sum (I_F(x_i) - \overline{I_F})(I_M(T_\mu(x_i)) - \overline{I_M})}{\sqrt{\sum (I_F(x_i) - \overline{I_F})^2 \sum (I_M(T_\mu(x_i)) - \overline{I_M})^2}}$$

where $\overline{I_M}$ represent the average grey-value and the sum is made over all voxels in the fixed image.

- Mutual information (MI): This kind of metric is often used when metrics such as MSD and NCC are not effective because we have images with different modalities (type of equipment used to acquire structural or functional images of the body) or with different grey values due to contrast agent for example. In these cases, we use metrics based on intensity statistics such as MI. we calculate the dependence from a statistical point of view like (based on the histogram and conjoint histogram):

$$MI = \sum_{a \in A} \sum_{b \in B} p(a, b; \mu) \log \left(\frac{p(a, b; \mu)}{p(a)p(b; \mu)} \right)$$

Where A and B are random variables corresponding to regularly spaced intensity bin centres.

These three metrics make sense because they give indications about the similarity between two images. Indeed two images are more likely to be similar if they have the same value at the same location and that's what is measured with the MSD et NCC metrics. On the other hand for images that do not have the same modalities, the grey level will not give a lot of indications about the similarity but the distribution of these values can give much more information and that is what we are looking for with the MI.

2.4 Optimizers

As we have seen in Figure 2.1 the registration can simply be seen as an iterative problem which goal is to minimize equation 2.1. We will try to find a search direction d_k such that $\mu_{k+1} = \mu_k + a_k d_k$ where a_k is a scalar gain factor controlling the step size along the search direction. An example for this kind of iteration is given in Figure 2.4.

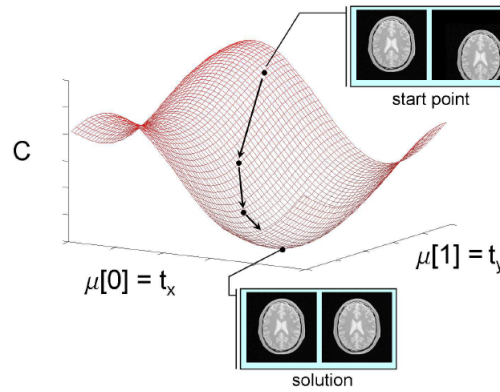


Figure 2.4: Example of iterative optimization for a translation [15].

In order to find the search direction several methods exist:

- Gradient descent: This is one of the most used methods in optimisation problems. This method will take as search direction the negative gradient of the cost function: $d_k = g(\mu - k) = \frac{\partial C}{\partial \mu}$.
- Robbins-Monro: It replaces the calculation of the gradient by an approximation: $g(\mu_k) = \tilde{g}_k$. This approximation allows faster computation.

2.5 Image samplers

Until now we were working with all the voxels by summing over all the voxels in the fixed image, but in order to accelerate registration it may be sufficient to work with a subset of voxels in this fixed image. There are different ways to select this subset:

- On a Grid. It is the same as downsample the image.

- At random: select voxels at random.
- At random location: coordinate between voxels can also be selected. It has the disadvantage that we will have to interpolate to find the grey value but it has the advantage of smoothing the cost function [15] and it is thus easier to find the best solution.

2.6 Multi-resolution

The goal of multi-resolution is to reduce the data complexity and the transformation complexity. We will then start the registration with images that are smoothed and/or downsampled. The data will therefore be less complex and the amount of data will decrease.

Several strategies exist:

- The Gaussian pyramid that smoothes and down-sampled the images.
- The Gaussian scale space that only smoothes the images.
- The Shrinking pyramid that only down-samples the images.

2.7 Summary

In this chapter we have seen the general operation of registration. We will now have to choose the metrics, transforms, optimizers, etc. in order to find the best transformation field while we will make a registration between our atlas and our target image. This transformation field will be applied to the masks of the OARs in order to find the contour of these OARs in the target image.

Chapter 3

State of the art

In this section we will briefly explain how image registration is used in radiotherapy and which methods already exist to make automatic segmentation of OARs and tumors.

3.1 Use of image registration in radiotherapy

One use of image registration is to match images of different modalities. Indeed, it is important to integrate image of different modalities (CT, MRI, PET, etc.) into treatment planning and plan delivery. Different modalities give different information about the anatomy of the patient but they can also show how tissues and organs are functioning. In this way, medical physicists and doctors will be able to see images of other modalities in the same geometrical position than the reference image (image on which treatment planning has been calculated).

A challenge in radiotherapy is the motion of organs and tumor due to patient breathing. This motion can lead to irradiation of zones that are not supposed to be irradiated. Image registration can be used in order to have the deformation field between an image of the patient before and after inhalation. We can then take into account this deformation field in the dose calculation during the planning phase.

A recent advance in radiotherapy is the image-guided radiotherapy (IGRT). In IGRT, an imaging technology is integrated in the radiotherapy machine. This allows to have images of the patient just before and even during the treatment. We can then use these images and the images use for treatment planning to find the best positioning of the patient. Indeed, image registra-

tion between these two images will give a deformation field. We can then apply this field to the patient to have the best position. Obviously, we can only apply translation and little rotation to the patient so the alignment will not be perfect and the use of non-rigid registration is useless.

Image registration can also be used for response assessment. Indeed, we can evaluate the response of the tumor or normal tissues to radiation by comparing images before and after treatment. Even if intuitively this can be done without the use of registration, it has been shown that it is often useful in order to compare functional imaging and soft tissue imaging [16].

Finally, image registration can be used for segmentation. We can simply use a single atlas or multi-atlas and registration to fit well known contours in an image to another image of another patient. This will be explained in more detail in the next section.

3.2 Methods for automatic segmentation

In addition to radiotherapy planning, delineation of anatomical structures is also needed in other domains such as surgery, where we try to be less and less invasive, location of pathology, diagnosis, etc. Nowadays the general approach to segment medical images is the manual delineation of the image by experts [17]. Unfortunately, this practice is relatively slow, hard to reproduce and expensive [18]. In this context efforts have been made in order to automate these tasks. In this section we will describe some of these methods with an emphasis on the process that uses atlases.

Some methods to segment images use only the information present in the image such as the intensity of each pixel or the presence of edges. Among these methods we can cite the segmentation by classification where each pixel is classified according to the features of the pixel. These methods use well known classifier methods such as thresholding, k nearest neighbor, Expectation-Maximization. Other methods that use image information are active contour, split and merge, region growing, watershed, etc.[17]. Unfortunately, in some situations these methods do not work. Indeed the difference in X-ray attenuation between soft tissues and other soft tissues or the tumor is small. They will thus have almost the same intensity and the algorithm has difficulties to catch the edge between the two tissues. However, this kind of methods can help to detect bones or lung that are very low/high contrast areas [12].

In this master thesis, we will mainly focus on methods that use atlases. An atlas is a reference image that has already been segmented. Most of the methods that use atlases work with the same underlying architecture:

- Generation of atlases
- Registration
- Atlas selection
- Label propagation
- Label fusion

Nevertheless, there are some differences between the algorithms such as the number of atlases used, the selection strategy or the label fusion strategy. Some examples of methods are described in Figure 3.1 and we will describe them hereafter.

At the beginning of atlas based segmentation, most of the time only one atlas was used. The segmentation problem was thus only a registration problem where we had to find the best transformation between the atlas and the images and then apply this transformation to the label to give the final segmentation. This method was for example used in 1995 in [19] in order to delineate anatomical structures of the human brain based on their appearance in MRI.

It has later been shown in [20] the critical effect of inter-subject variations while we use only one atlas for segmentation. They proved that the use of a single atlas to segment structures in the brain will not lead to good results because of the variability. Nevertheless, they said that atlas based methods are a valid approach for this kind of problem, but that we should use several atlases to achieve good results.

As we can see on Figure 3.1, even when we use several atlases multiple methods exist. In a paper of 2003 ([21]), Rohlfing compares four approaches: the use of an individual atlas, the use of the best atlas after affine registration according to the normalized mutual information (NMI), the generation of an average shape atlas subsequently used during registration and finally the use of multiple atlases and a majority voting fusion (the label of one pixel is chosen as the label that is the most represented in the atlases at the same place after registration). They used the four methods to segment confocal

microscopy images of bee brains. This study shows that the use of the last method leads to the best result, followed by the use of an average atlas while both methods that use a single atlas show poor results.

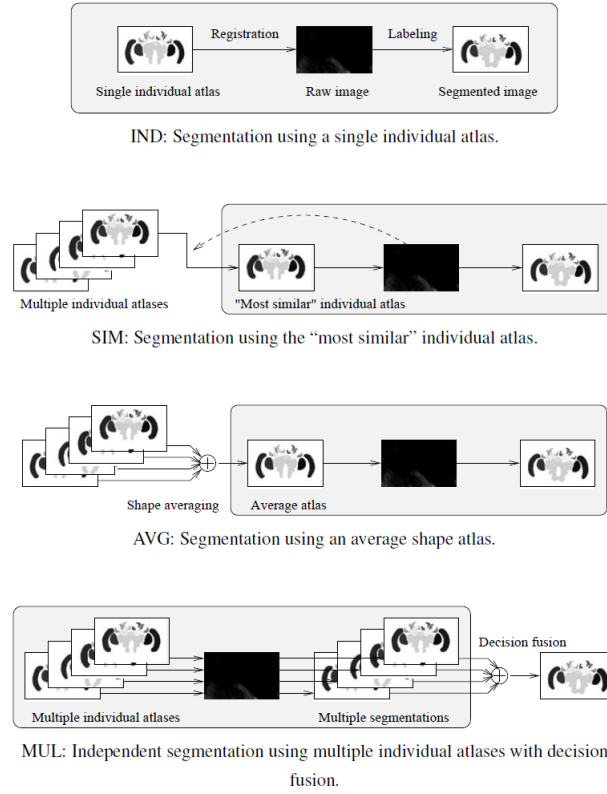


Figure 3.1: Different methods for atlas based segmentation [22].

During the same period other papers show results that go in the same direction. For example, in [23], motivated by the identification of OARs for application in radiotherapy, Park and al. constructed a probabilistic atlas of the abdominal region. They registered this probabilistic atlas on a novel image in order to find the contours of four different organs in this novel image. This method had the advantage of working in a single coordinate frame and to require only a single registration for a new image. This study shows improvement over other standard methods in the abdominal region.

Concerning the simple idea of multiple atlas segmentation in [24] or [25], the authors use also registration of multiple image and a majority voting in

order to label different brain structures. Once again, these studies show good results compared to single atlas segmentation. These papers together with the paper of Rohlfing and al. ([21]) are pioneers in the use of multi atlas segmentation.

After this proof of concept, efforts have been made in order to improve the results given by multi-atlas segmentation. One of the ideas that emerged was the idea of atlas selection. Firstly, it will decrease computation time. Indeed, a bottleneck in atlas based segmentation is the non-rigid registration that is very time consuming. If we made a selection before this non-rigid registration it will reduce the time consumption because the number of registrations is proportional to the number of atlas. Secondly, by selecting the best atlases, we will most probably remove the most irrelevant ones. In [26] and [27], Aljabar and al. compare different fusion strategy to label structures of the brain on MRI image. They compare the selection based on segmentation similarity (DSC between true segmentation and atlas segmentation), based on some image similarity (SSD, CC, MI, NMI) and based on demographics (age in this case). They compare results given by their selection against a random selection of the same number of atlas. The selection based on segmentation gives the best result, but it is not really feasible in reality because we are not supposed to have the segmentation already. The two other methods also show improvement compared to random selection with a mean best case while using NMI similarity. Other studies, like [28] also compare different types of similarity measures for atlas selection, but this time in the pelvic region. This study suggests that an atlas selection based on SSD gives the best result. In most cases the number of atlases that are going to be used is estimated but in some case like in [29] the atlas are automatically selected and registered one by one until no more improvement is expected.

As we mentioned before, the registration step is a very time consuming step. In this context some researchers tried to find methods that will improve processing time. A first method is already described before and simply consists in decreasing the number of atlases thanks to a selection. Another method to encounter this problem was introduced in [30] by Artaechevarria and al. with the concept of "one registration, multiple segmentations". This method is based on the fact that we can approximate a transformation from an atlas to a query image as the composition of the transformation of the atlas image to a reference image and the transformation of this reference image on the query image. Thanks to this hypothesis, we simply have to make one online registration between the query image and the reference image to find the transformation between the query image and all the atlases because

registration between the atlases and the reference image were already done offline. This method shows poor results compared to normal multi-atlas algorithms, but with a large gain of time.

With the growing number of atlases available, it could be important to make a selection of atlas before any registration. This could be done by clustering the atlas in order to put together atlases that fit well together. A cluster method is used in [31]: all atlases are registered one to each others and the results of these registrations are estimated thanks to DSC between them. Then atlas are clustered so that each group contains atlases that register well together. We then register the query image to the representative of each cluster and choose the cluster where the registration gave the best result. In [32] Shi and al. also used cluster, but here they make different clusters for each region of the brain that they tried to segment.

The last step where we can try to increase the precision is by changing the label fusion algorithms. We have already talked about majority voting where the same weight is given to each atlas and each pixel contains the label that occurred most often among the labels assigned to this pixel in the wrapped atlas. In [30] a weighted voting method is introduced by Artaechevarria and al. In this method a weight is given to each atlas according to the mutual information between the query image and the atlas. They tested their method on MR images of mouse brain and while it gave better results than majority voting, the improvements were not impressive. In [33] Isgum and al. also give weight according to the registration success. They want that an atlas that was more successfully registered to the query image contributes more than atlases that registered less successfully. In order to know the success of the registration they compute an absolute difference of image intensity. The biggest difference with the previous paper is the fact that they compute these weights locally and not globally as before. In most of the weighted fusion methods, the weight is computed independently for each atlas and it did not take into account the fact that different atlases can lead to identical label error. This problem was solved in [34] by Wang and al. where the weight of each atlas is computed locally and depends on a dependency matrix that take into account all the atlases at the same time.

We can note that for most of the methods described before, the atlases used are atlases delineated by hand by experts. Nevertheless, it is also possible to add in the atlases those computed by the algorithm but we have to be careful because they are probably less good than manually segmented atlases. We could for example give them less weight during the fusion algorithm

because they are less reliable.

3.3 Summary

In this chapter we have seen why registration is a relatively important tool in medical imaging and especially in radiotherapy. After that we took a look at methods that can be used in order to automatically segment region of interest in medical images with a focus on methods that used atlases and registration. Concerning this last point we have seen the path in order to arrive at methods that we use nowadays. Finally in the remainder of this thesis we will try to use and compare several of the methods described above in the pelvic region in order to segment the bladder and the rectum in prostate cancer patient.

Chapter 4

Segmentation using atlas-based registration

4.1 Materials

The goal of this master thesis is to register atlases on a query image in order to find the contour of different organs in this image. The images that we use are 3D anatomical images of patients treated for prostate cancer. The 3D image is a composition of several 2D images that are slices of the patient acquired via a CT scan. The images are in DICOM format. To accompany these images, each patient has also a 3D DICOM Structure (RTSTRUCT) that contains all the contour of the tumor and OARs. In this master thesis, we will work with 20 different 3D images of 20 patients and we will run our algorithm on 10 of these patients by registering the 19 other atlases on each patient using a leave one out method. We can find slices of each of these images in the three plans in appendix A

Such images can be visualized thanks to programs such as Slicer 3D¹, vv², etc. An example of an image that we used is visible in Figure 4.1. In this master thesis, we test atlases method for patients that suffer from prostate cancer so our images are images of the pelvic region. In this region we can find the bladder, the rectum, the hip bones, the prostate and the anal canal. An anatomical board of the region can be visualized on Figure 4.2. The contour of the body, of each organ and of the tumor were drawn manually on these images by a physicist of the hospital.

¹<https://www.slicer.org/>

²<https://www.creatis.insa-lyon.fr/rio/vv>

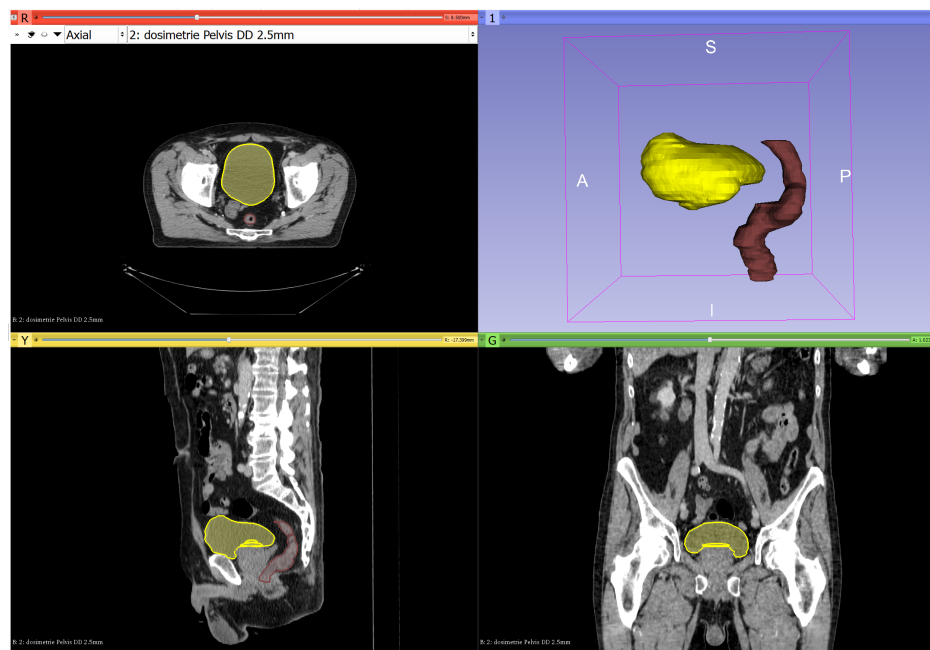


Figure 4.1: Example of 3D view of a patient on slicer 3D. We can see the bladder in yellow and the rectum in brown.

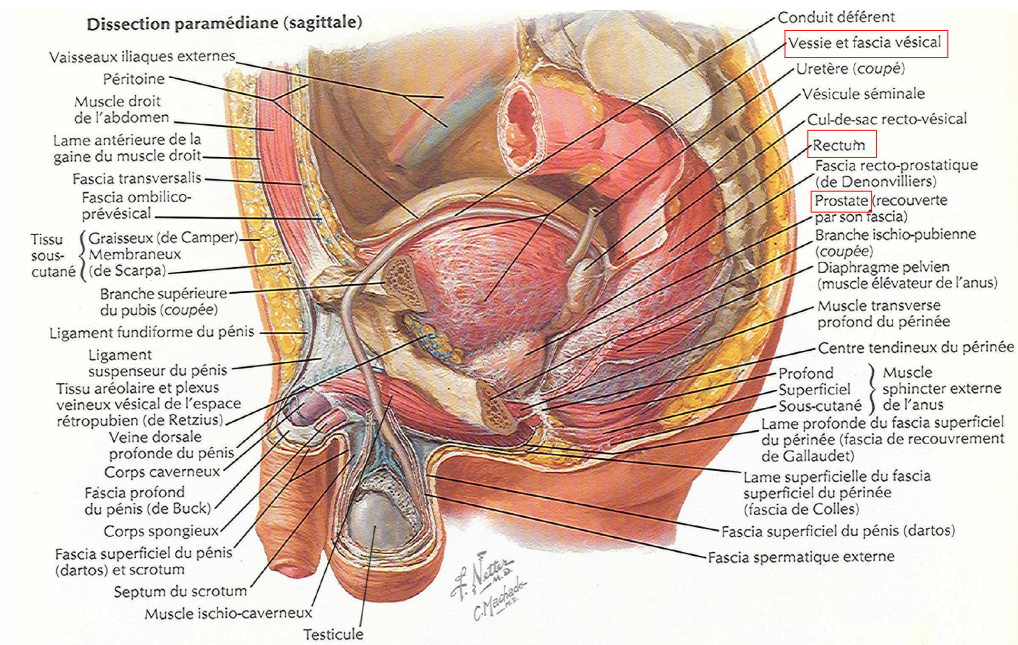


Figure 4.2: Anatomical structure in the pelvic region [35].

In these pictures we can also see the table of the scanner. While we will use the images, we will use a mask on the body region to not take into account this table in our calculations.

Because all the images are of the same modality, the same structure in different image will often have approximately the same grey level as for bones that are very bright. Nevertheless, in some case there can be large differences due to contrast agent or due to the presence of prosthesis that will create some artifacts. These artifacts are potentially a source of error during registration since they introduce large differences between grey level in the images. This phenomena can be seen in Figure 4.3.

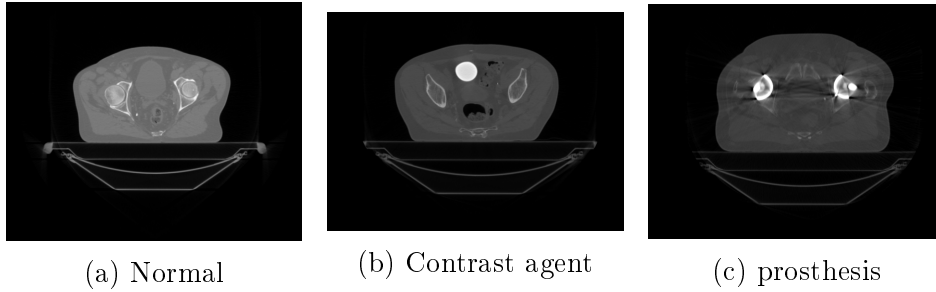


Figure 4.3: Example of changes in the grey level between patients. This introduces difficulties for the registration.

All the images are given by the CHU-UCL Saint-Elisabeth of Namur with the approbation of their ethics committee.

Concerning the registration steps they are done thanks to SimpleElastix³ that is an extension of SimpleITK that includes the popular Elastix C++ library. Elastix is a toolbox for registration that allows the users to configure registration method for specific applications. [14].

The CBCT simulation are done with the open-source REGGUI package that is an image processing open-source platform for adaptive proton therapy in cancer treatment⁴.

Finally all the calculations are made on a personal portable computer running on Windows 10 x64, Quad core with a processor Intel Core i7-4510U (2,0 GHz) and 8GB of RAM .

³<http://simpleelastix.github.io/>

⁴<https://openreggui.org/>

4.2 Methods

As mentioned before, the goal of this thesis is to automatically find the contour of organs in the pelvic region on query images thanks to images that have already been segmented by experts (the atlases). The main idea behind the process is to use registration between the query image and each atlas. The result of the registration will give us a deformation field that we will apply to the contour of each organ in order to have an approximation of the contour of these organs in the query image. In this thesis, we will use a multi-atlas based segmentation. This method has already shown good results in some anatomical region such as the brain. Because we will use several atlases we will also have to implement methods to fuse the labels.

A general method is visible on figure 4.4. In a first step we will make a rigid registration of each atlases on the query images. Because the non-rigid registration step is known to be a very time consuming step, especially for large 3D images, we will make a selection of the best atlases before this step in order to use a minimum number of atlases that will lead to the best result. When the atlases are selected, we will make the non-rigid registration of the selected atlases on the query images. Finally, we will make a fusion of the potential contours in order to find the best contour. To sum up we will divide the algorithm in three main components:

1. The two **registration** steps: the rigid registration at the beginning and the non-rigid registration after the atlas selection step.
2. The **atlas selection** step.
3. The **label fusion step**.

we will explain these steps in more detail below.

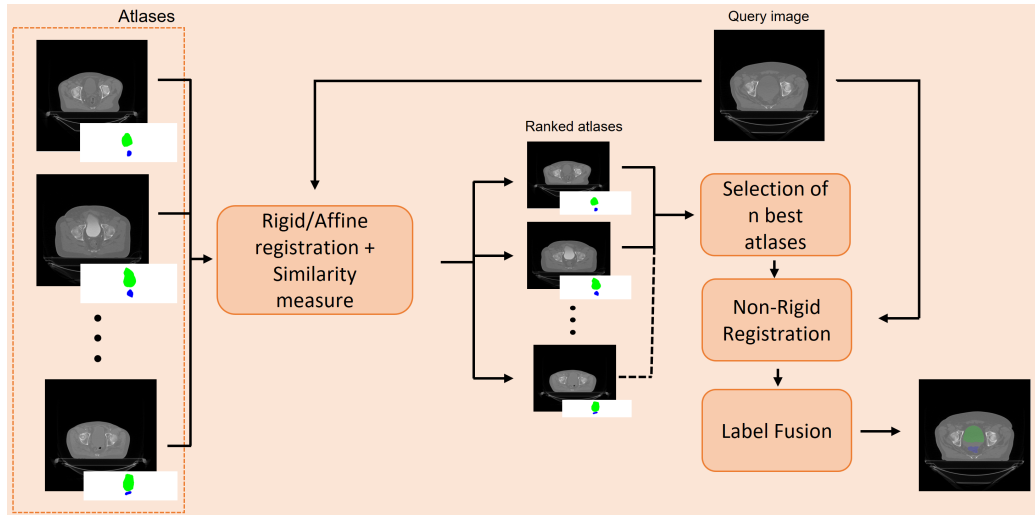


Figure 4.4: Multi-atlas segmentation method. We can see slices of our image and their associated atlas with a mask of the bladder in green and a mask of the rectum in blue.

4.2.1 Registration

We have already seen in chapter 2 how image registration worked. We have seen that there are some parameters that must be fixed. We use the default parameters map of Elastix 'rigid' and 'bspline' that use the following parameters:

- The **transformation**: The rigid registration will be a simple 'rigid' registration while the non-rigid one will be a 'B-splines' transformation.
- The **interpolator** is a linear interpolator.
- We use as **optimizer** a gradient descent optimizer.
- The **image sampler** is a random coordinate sampler.
- We used Gaussian scale space with three resolution ($\sigma = 4.0, 2.0, 1.0$ voxels) for the **multi-resolution strategy**. This strategy only smoothes the images but does not down sample them. Intuitively, we could think that it is important to down sample the images to win some time in the registration, but since we already used an image sampler that selects a certain amount of voxels no matter the size of the image it is not useful to down-sample it again.

- As **metric** intuitively, we would choose a mutual information metric since the grey level is not the same in all the picture often because of the use of contrast agents. This is visible in Figure A.13 compare to other image Appendix A To validate this hypothesis, we will compare the use of a mean squared difference metric and the use of a mutual information metric.

Unfortunately, registration and especially the non-rigid registration is a very time consuming step. For a 3D image such as the one that we used it takes approximately 1400 seconds (23 minutes). Knowing that we make 19 registrations on each of the 10 patients this number becomes very large (3 days in sequential execution on specified hardware. Note that parallel execution on multiple patient data seems possible since overall CPU usage seems to be less than 50%). In this context, for the test that concerns registration, we will work with 2D images that are slices of the 3D image that we have. We chose a slice where we can see the bladder and the rectum at the level of the femoral head. An example of such a slice is given in Figure 4.5.

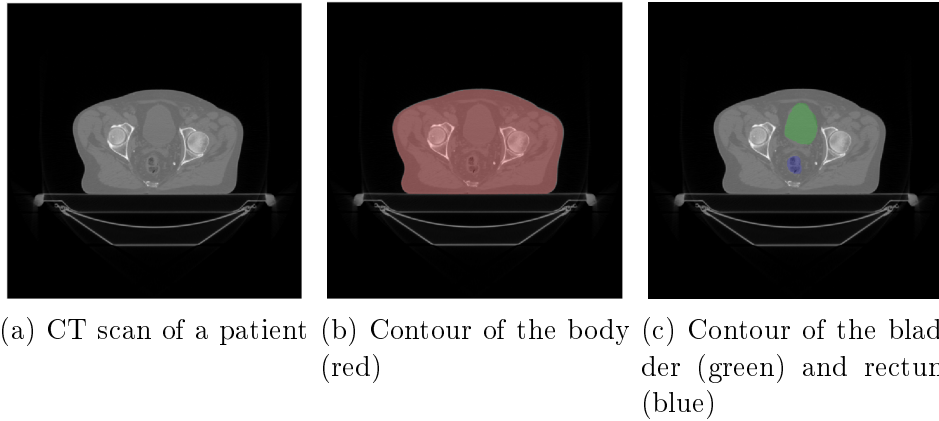


Figure 4.5: Example of a slice of a patient and his associated atlas.

We manually extracted one slice for each of the 20 patients. As for 3D images, ten of them will be used as query images while all of them will be used as atlases, the query image will be left out (leave one out method).

To compare the different methods we compute the dice similarity coefficient (DSC). The DSC is computed between automatically labeled region and manually labeled region. Indeed, even if we consider that we do not have the label of the query image during the algorithm, we have it in reality, so we can compare the region drawn by physicians (TL(True Label)) with the

region found by our algorithm (AL(Automated Label)) with the following formula (note that AL and TL are binary images):

$$DSC = \frac{2|TL \cap AL|}{|TL| + |AL|} \quad (4.1)$$

Where $|\cdot|$ is the number of pixels that are equal to 1. This metric will give us an idea of the similarity of our result with the contour drawn by the physicians. This value can be equal to 0 if there is no overlapping between the two regions and it will be equal to 1 if the two regions are perfectly overlapping.

4.2.2 Atlas selection

The atlas selection step consists in selecting a certain number of atlases before the non-rigid registration step. There are two main reasons to make an atlas selection step:

- There will be less atlases that will be registered on the query image so we will gain a lot of time.
- By choosing the best atlases we will put aside atlases that could have lead to bad contour predictions. For example atlases that have large differences with the query image will probably be excluded during this step.

In order to take into account this second advantage we will rank the atlases. If we choose a good ranking method we will exclude the atlases that would have lead to bad result and include the atlases that lead to the best result.

In this master thesis, we will compare three different methods to rank the atlases:

1. Based on the sum of square difference (SSD) between the query image and the atlas.
2. Based on the mutual information (MI) between the two images.
3. Based on the similarity with a model. This method is a bit more complex and relies on the fact that an atlas that has almost already the same contour as the real contour will probably lead to better result. Unfortunately, we don't have the real contour of the region in the query image so we will try to construct a model of this contour to compare

with the contour given by each atlas. In order to construct this model we simply made a majority voting fusion of all the atlas after rigid registration. We then compute the dice similarity coefficient between the model and each atlases to rank the atlas.

Once we have ranked the atlases we still have to determine the number of atlases that lead to the best result. Note that different atlases will be used according to the region that we want to delineate.

4.2.3 Label fusion

The Label fusion step is the last step of our algorithm. In this step we will try to determine the contour of each organ in the query image based on the contour given by each of the registration. The goal is to combine the different results to give a better result.

Several methods exist to make this label fusion and in this master thesis, we will compare some of them:

- Majority voting fusion: it is the simplest case of fusion in multi-atlas segmentation. Each output pixel contains the label that occurred most often among the labels assigned to this pixel in all the atlases. In other words a pixel will be labeled as an organ if he is part of this organ in a majority of the atlases after the non-rigid registration.
- Weighted voting method: The concept is the same as for majority voting fusion except that this time we will give a weight to each atlas according to the confidence that we have that an atlas is far or near of the real solution. We will test different ways to give a weight:
 - According to the mutual information (MI) or to the sum of squares difference (SSD) on the entire image.
 - According to the mutual information (MI) or to the sum of squares difference (SSD) on the neighborhood of the target organ.

In order to compare our results at each step, we will start by the easiest method that is simply a majority voting method with the 19 atlases. After each step we will continue with parameters that give the best result at the previous step.

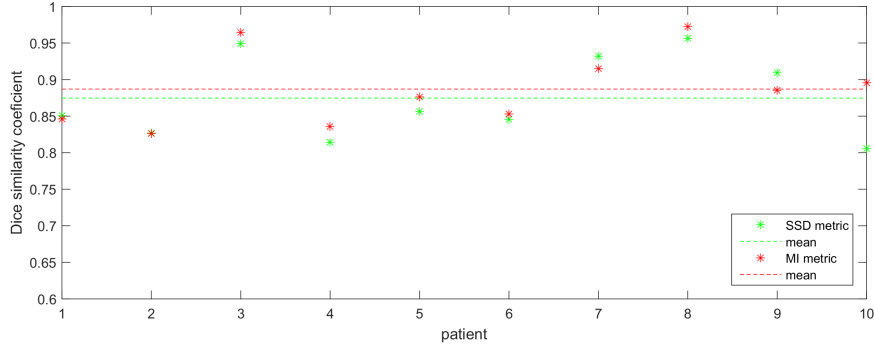
4.3 Results and discussion

In this section we analyze the results given by the different methods described in the previous section. We test our algorithm on two main organs of the pelvic region: the bladder and the rectum. These two organs are quite well representative since one of them is quite big and the other is smaller. Moreover, both have very different shapes and sizes according to the patient that we are looking at and this is especially true for the rectum that can have different grey-level on the CT scan.

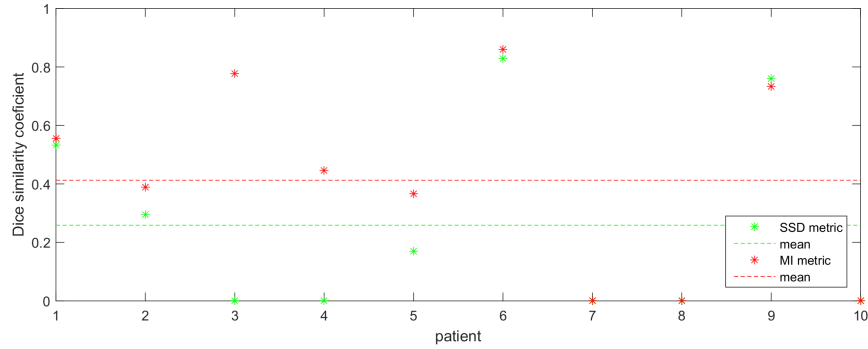
Note that for patient 8 we don't have the contour of the rectum so we exclude this patient and work with only 9 patients.

The first thing that we are going to compare is the choice of the metric for both registration steps. We will compare a sum of squares differences metric with a mutual information metric. We can see the results on Figure 4.6 . The values for the SSD metric are visible in green and those of MI metric in red. For the bladder we can see that there is no huge difference between the two metrics, MI gives better results only in six cases out of 10. The mean DSC over the 10 patients increases slightly from 0.8747 ± 0.018 to 0.8870 ± 0.0161 (mean $\pm$ standard error of the mean ($\frac{\sigma}{\sqrt{n}}$)). Concerning the rectum on Figure 4.6b we can see that MI seems more convincing with only one result better for the SSD metric and a mean that goes from 0.2587 ± 0.1052 to 0.4128 ± 0.1039 .

As we can see the atlas-method seems to work better for the bladder than for the rectum. This difference can be due to two main reasons. Firstly, the bladder is bigger than the rectum and the registration is based on metrics that will compare the images according to the difference between their pixels. If a region contains more pixels than another, it is more likely that the registration will be more focus on this region because the overall difference between the two images will be lower if two big regions fit well than if two small regions fit well. Secondly, the bladder has a smoother grey-level and it is thus easier to compare them to a bladder in another image. On the contrary the rectum can have very different aspects, this can lead to large differences in the metric even if they are well aligned in reality. This is probably also the reason why the MI metric gives much better results on the rectum.



(a) For the bladder.



(b) For the rectum.

Figure 4.6: Comparison of SSD metric and MI metric.

As we expected, the mutual information metric gives slightly better results so we will use this metric to make the 3D registration. However the 3D non-rigid registration remains a very time consuming step and we can notice on Figure 4.7 that the part of the image with the organs that interested us in this thesis is between the two red lines and takes approximately one third of the entire image. We then decided to extract manually for each patient the region of interest and to work with smaller 3D images. Thanks to this simplification the registration time decreases from around 1900 seconds to 550 seconds per registration. We can also compare these times with 2D registration where it takes around 90 seconds to register a single slice. If we had to register each slice of a 3D image of around 150 slices it would take 13500 seconds (3h45).

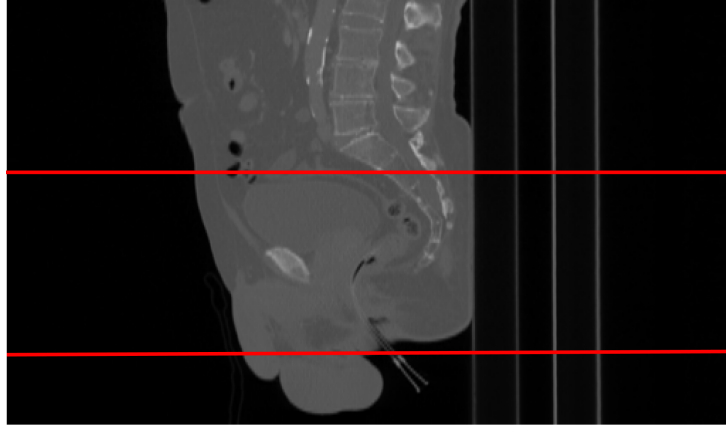


Figure 4.7: The interesting part of the 3D image is between the two red lines and represents approximately one third of the entire image.

Moreover, in Figure 4.8 we compare the result obtained by the fusion of 19 atlases on each of the 10 patients if we made the registration on the entire image or on the selected part only. For the bladder we have a DSC of 0.7127 ± 0.00384 for the entire image and it increases to 0.7946 ± 0.00323 with the part of the image. On the contrary, for the rectum it goes from 0.4682 ± 0.0587 to 0.3996 ± 0.00804 . We also compare 2D registration slice by slice with 3D registration. We do that for a single patient because of the time that it already takes to make the 2D registration slice by slice. For this patient we have a DSC for the reconstruction of the bladder slice by slice of 0.8088 and of 0.8561 for the 3D registration. Concerning the rectum it goes from 0.4952 with the concatenation of 2D slices to 0.7353 for 3D registration.

Taking everything into consideration we preferred to continue working with the interesting part of the image and 3D registration.

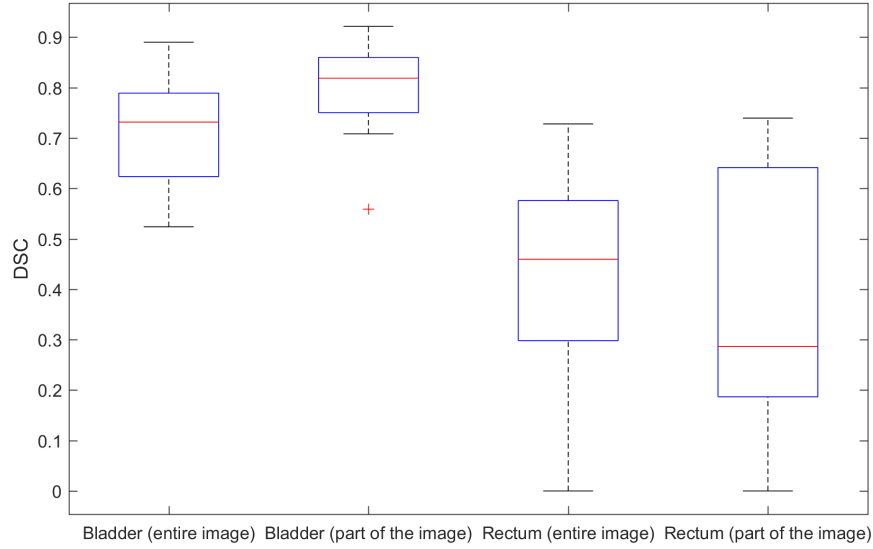


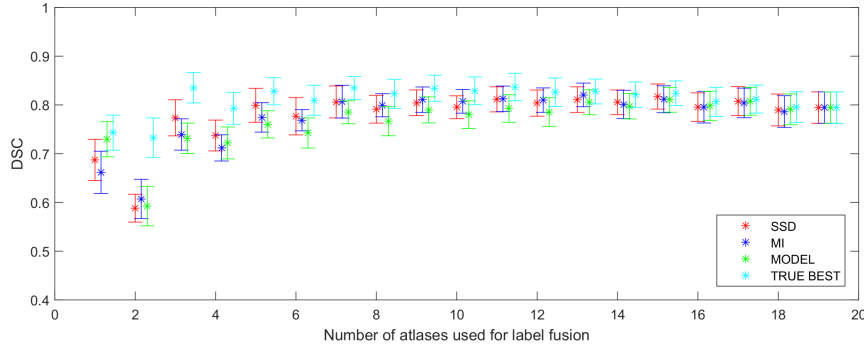
Figure 4.8: Boxplot of the Dice similarity coefficient for the ten query images. The red line represents the median and the edges of the box indicate the 25th and 75th percentiles.

Now that we have chosen the parameters for the registration, we continue with the second step that is the atlas selection. In this step we have to choose on which criterion we will rank the atlases and then choose how many atlases we will use during the non-rigid registration. We compare the result obtained by each of the methods described previously with a fourth method that takes the atlases that have the best DSC with the real contour after rigid registration. Obviously this can only serve as a comparison because in real cases we do not have access to the real contour so we cannot compute the DSC.

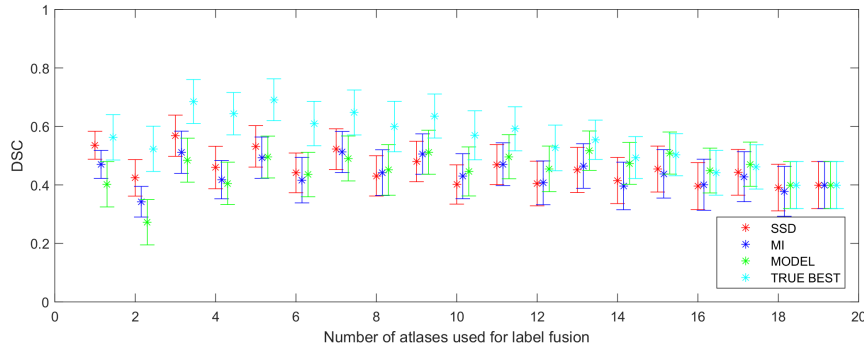
The results are visible on Figure 4.9 and summarized in table 4.1. The selection based on the true DSC after rigid registration gives better results than the other methods. This is more true for the rectum where the DSC is 11% higher than any other methods so we can conclude that for the rectum it is difficult to automatically detect the atlases that are going to lead to the best result. On the contrary, for the bladder it seems that the DSC stays quite near with only an increase of 1% for the best cases.

If we look at the result for the bladder, we can see that the DSC are very close for the SSD and the MI methods and that the model based method

seems to be a little less performing. The best result is achieved by the MI method with 13 atlases. However to win some time we can work with 10 atlases since the DSC seems to be quite constant from 10 to 15 atlases. Concerning the rectum it seems that the SSD method gives the best result when used with a small number of atlases but when we use more than eight atlases then the model based method seems to outperform the two other methods every time. For the rectum the best result is given by the SSD method with 3 atlases. One way to have better results could be to increase the number of atlases before rigid registration. We currently work with 19 atlases but if we increase this number, we are more likely to have atlases that will represent all the variations that the rectum and bladder can have. Consequently if atlases are more similar, there will be less errors in the registration and more similarity after non-rigid registration leading to better results.



(a) For the bladder



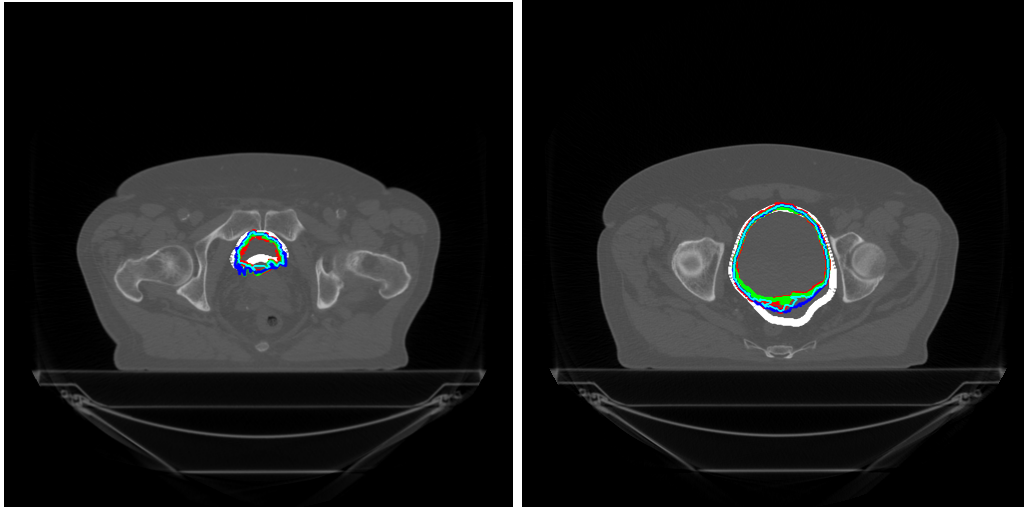
(b) For the rectum

Figure 4.9: Comparison of different ranking methods and number of atlases to select. The * represents the mean over the ten patients and the bar represents the error on the mean.

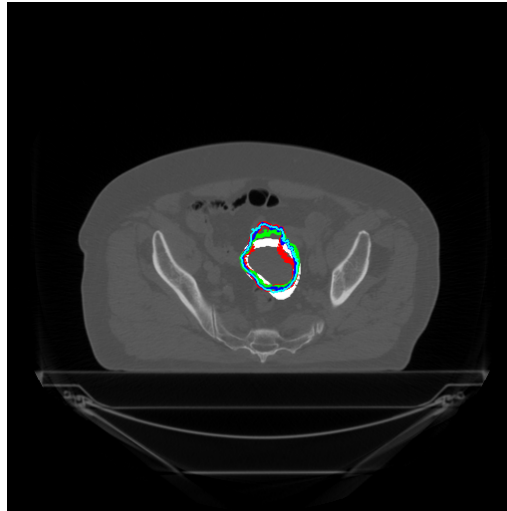
Method	Bladder		Rectum	
	Best DSC	Number of atlases	Best DSC	Number of atlases
SSD	0.8173	15	0.5682	3
MI	0.8206	13	0.5125	7
MODEL	0.8105	15	0.5172	13
DSC with real image	0.8367	11	0.6913	5

Table 4.1: Best DSC obtained with each method and the number of atlases needed to obtain this DSC.

In addition to the numerical values one can also see what each method will give visually on a patient. In Figure 4.10 we look at the result for the bladder with 10 atlases in three different slices of the bladder, one at the bottom, one at the middle and the third at the top of the bladder. We can see that it does not fit perfectly the real contour of the bladder but that it gives an idea about the shape and localization of the bladder. Moreover it is difficult to see a real difference between the results given by the different methods. We can make the same exercise in coronal (Figure 4.11) and sagittal (Figure 4.12) slices. Once again we can see that the results are much better in slices that are in the center of the bladder than in slices at the extremity where in some cases there is no contour found by our algorithm such as in Figure 4.11c and 4.12a.



(a) Slice at the bottom of the bladder. (b) Slice at the middle of the bladder.

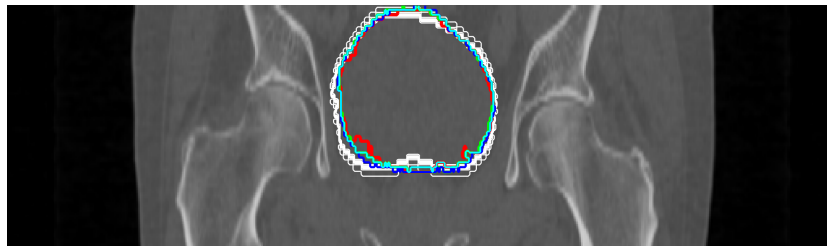


(c) Slice at the top of the bladder.

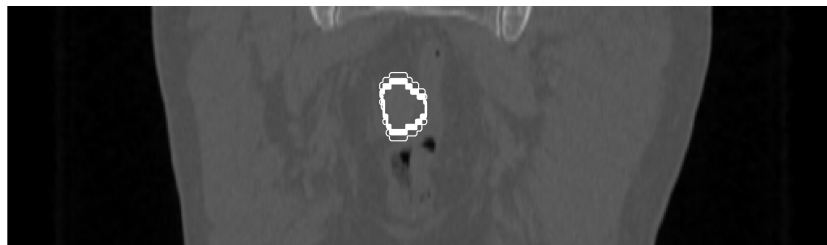
Figure 4.10: Visual comparison of different methods of selection on different transverse slices of the same patient with ten atlases. We have in white the contour drawn by an expert and in red, green, blue and cyan respectively the SSD method, the MODEL method, the MI method and method based on the DSC with the true label.



(a) Slice at the front of the bladder.

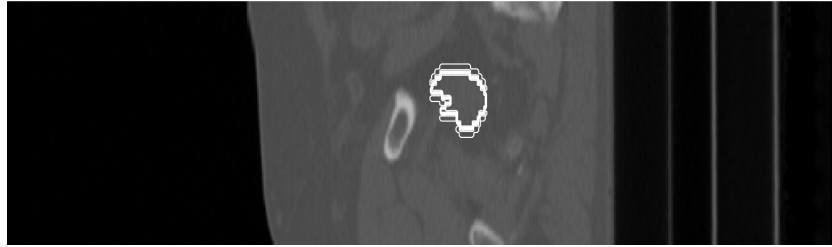


(b) Slice at the middle of the bladder.

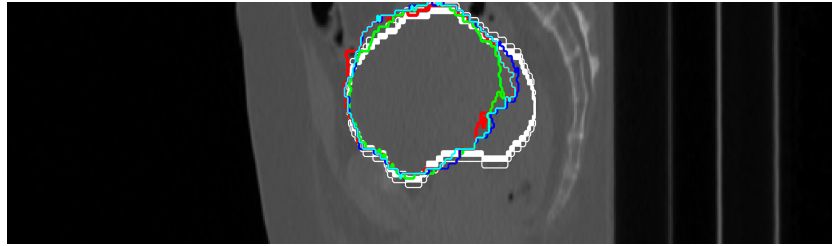


(c) Slice at the back of the bladder.

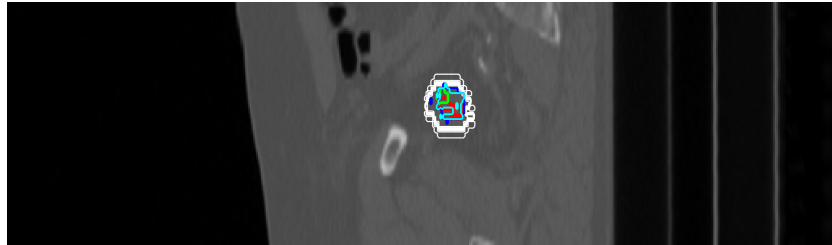
Figure 4.11: Visual comparison of different methods of selection on different coronal slices of the same patient with ten atlases. We have in white the contour drawn by an expert and in red, green, blue and cyan respectively the SSD method, the MODEL method, the MI method and method based on the DSC with the true label.



(a) Slice at the left of the bladder.



(b) Slice at the middle of the bladder.



(c) Slice at the right of the bladder.

Figure 4.12: Visual comparison of different methods of selection on different sagittal slices of the same patient with ten atlases. We have in white the contour drawn by an expert and in red, green, blue and cyan respectively the SSD method, the MODEL method, the MI method and method based on the DSC with the true label.

We can also look at slices of the rectum in the three plans in Figure 4.13.

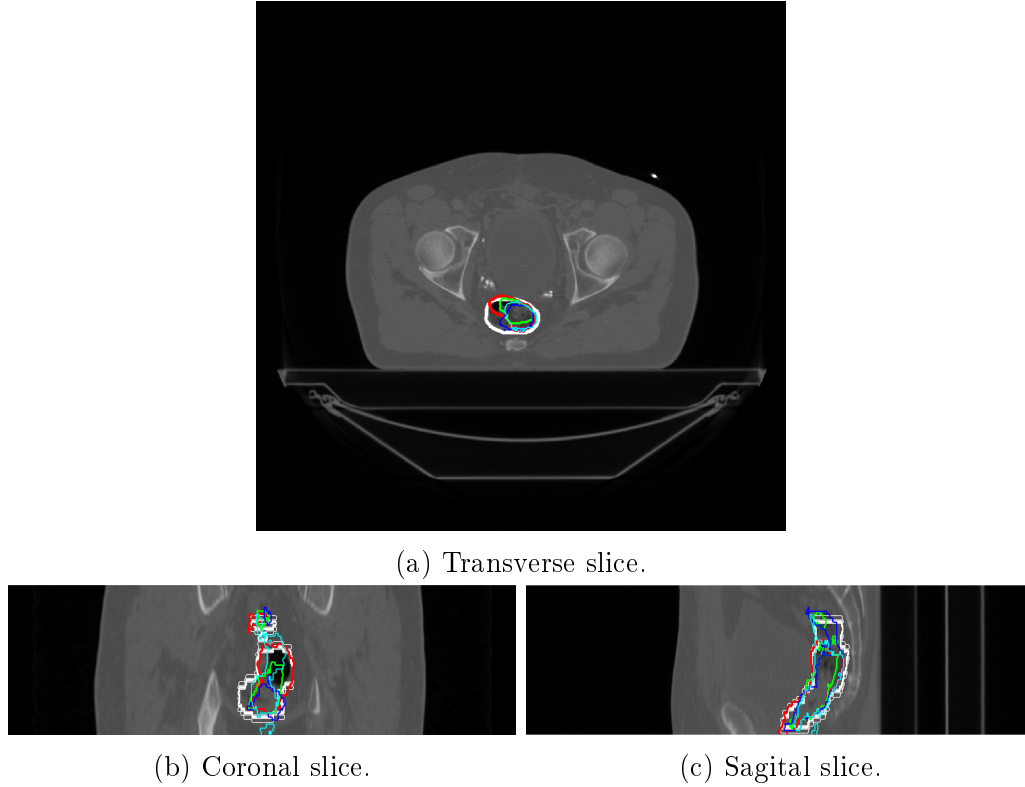


Figure 4.13: Visual comparison of different methods of selection on different slices of the same patient with three atlases. We have in white the contour drawn by an expert and in red, green, blue and cyan respectively the SSD method, the MODEL method, the MI method and method based on the DSC with the true label.

The goal of the atlases selection was to choose the atlases that are more likely to give a contour after non-rigid registration that is near the real contour in the target image. We will thus compare the best methods found for the bladder and the rectum with a method that chooses the atlases having the most similar contour with the target image after non-rigid registration. In order to do that we compute the DSC between the contour found thanks to each atlas after non-rigid registration and the real contour. Once again it is not feasible in real situation because we used the fact that we have the contour drawn by an expert. Moreover the selection is made after non-rigid registration so we will not have the benefit of skipping the non-rigid registration for the rejected atlases and we will not decrease the computation time.

The comparison is visible in Figure 4.14. We can see that for the bladder the mean increases from 0.8206 ± 0.024 to 0.8660 ± 0.013 . For the rectum the increase is bigger, we go from 0.5682 ± 0.074 to 0.7209 ± 0.029 . We can say that for the bladder, the selection is relatively good because the DSC increases by only 4%. On the other hand for the rectum we have an increase of almost 16% that shows that it is relatively difficult to find a good selection method.

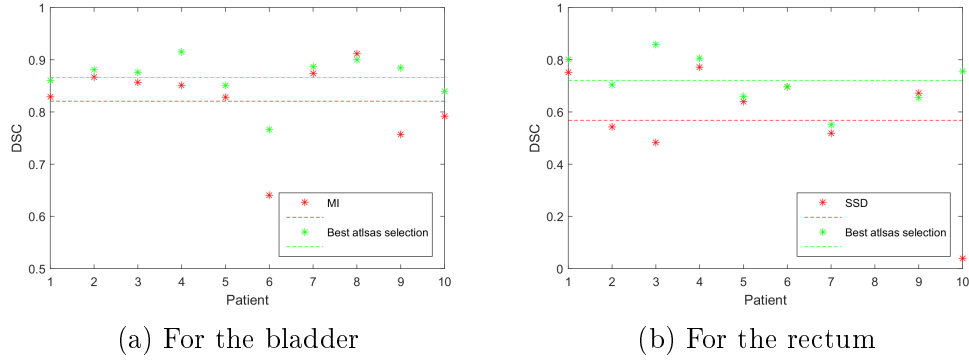


Figure 4.14: Comparison of our selection method with a selection based on the atlases that have the most similar DSC after non-rigid registration. The dotted lines represents the mean over all the patients.

Now that we have selected a certain number of atlases, we will try to change the fusion method in order to improve our results. Until now we used a simple majority voting fusion which means that each atlas has equivalent weight and that a pixel will be labeled as an OAR if it is labeled as this OAR in the majority of the atlases. We can write it mathematically as:

$$p(l|\mathbf{x}, QI) = \sum_{i=1}^n w_i * p(l|\mathbf{x}, A_i)$$

where $p(l|x, QI)$ is the probability of having the label l at location $\mathbf{x}$ in the query image (QI), w_i is the weight given to the atlas ($\frac{1}{n}$ for majority voting) and $p(l|x, A_i)$ is the probability of having the label l at position $\mathbf{x}$ in the i th atlas (0 or 1 in our methods). Finally a pixel is labeled as label l if $p(l|x, QI)$ is greater than 0.5.

In this part we will try to change the weight w_i of each atlas in order to have better results. We compare several methods:

- Based on the sum of squared difference: $w_i = \frac{1}{SSD(QI, A_i)}$. We used the inverse because the SSD is smaller if the images are closer.
- Based on the mutual information: $w_i = MI(QI, A_i)$.

In these cases the weights are the same for the rectum and the bladder while atlases will not necessarily give the same result for both OARs. In this context, we will also try to give the weight according to the SSD and the MI in the neighborhood of each organ.

We can see on Figure 4.15 the DSC given by each of these methods for each patient. Unfortunately, there is no huge increase in the DSC when we used weighted voting fusion. We can conclude the same for the rectum by looking at Figure 4.16.

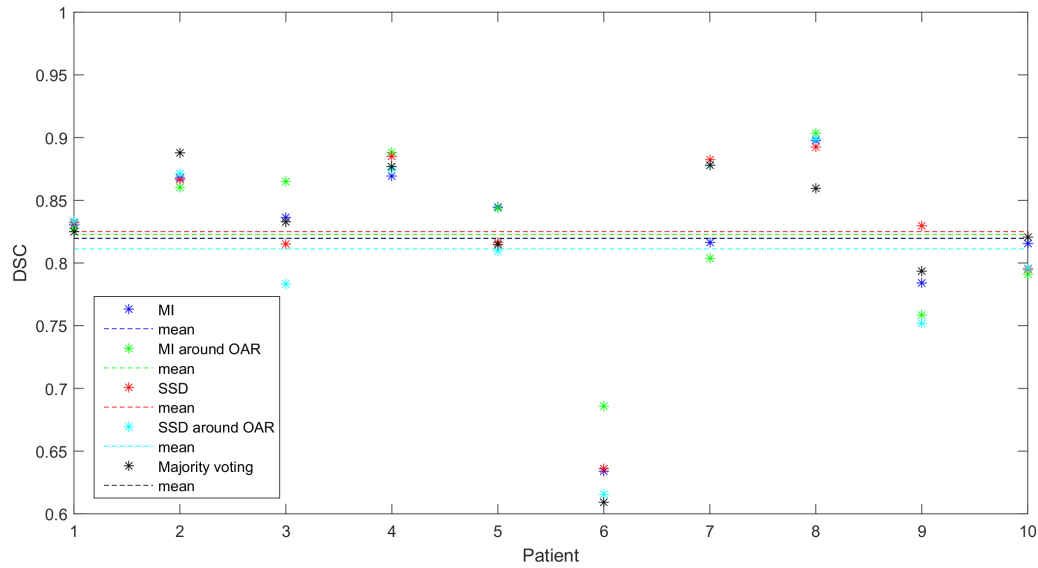


Figure 4.15: DSC for the bladder on our ten patients after using different methods of fusion algorithm. The mean of each method is represented in dotted lines.

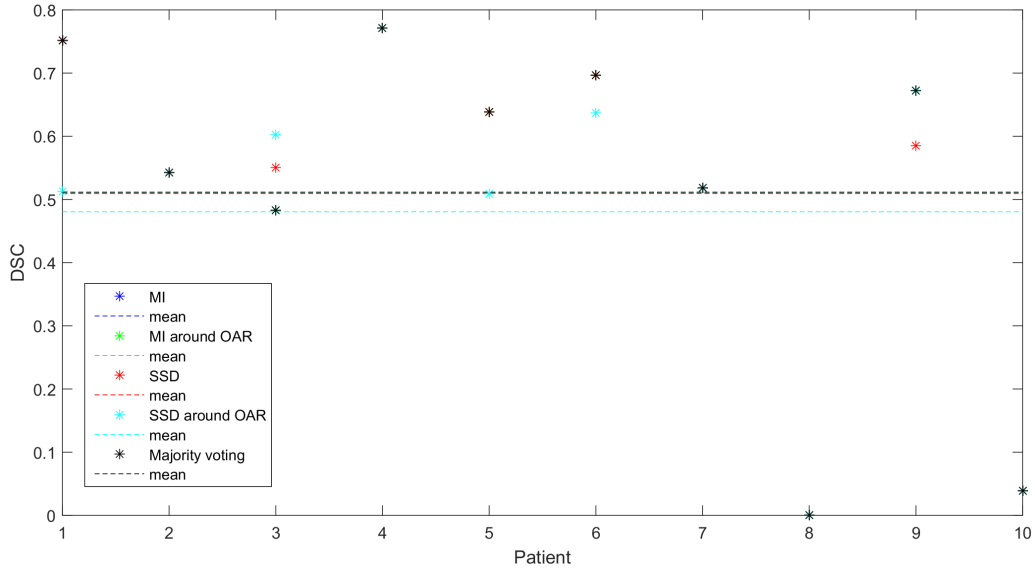


Figure 4.16: DSC for the rectum on our ten patients after using different methods of fusion algorithm. The mean of each method is represented in dotted lines.

We can see that in most of the CT scans that we have, we can easily spot the bladder. So maybe we can simply use a thresholding on the grey level of the bladder in order to contour it. We try this method and compare the result obtained with the result obtained by the atlas based method.

We chose the threshold by looking at the standard values of the grey level of the bladder. In a majority of the cases the grey level takes values between -30 and 40. We then decide to keep only the values between these two limits. We then use morphological operations (opening, closing and dilation) to keep only the bladder and remove other soft tissues that could have been in the thresholding region. We can see in Figure 4.17 an example of this method step by step. The results given by this method are shown in Figure 4.18 and are compared to the result given by the atlas based method.

We can see in this Figure that the thresholding method gives better results than the atlas based method in 7 cases out of 10. It clearly outperforms the atlas based method in term of DSC but also the computational time is much shorter for this kind of method. It takes around 4 seconds to make the segmentation while it took already 550 seconds just to make one registration with the atlas method and we have to do minimum 10 registration.

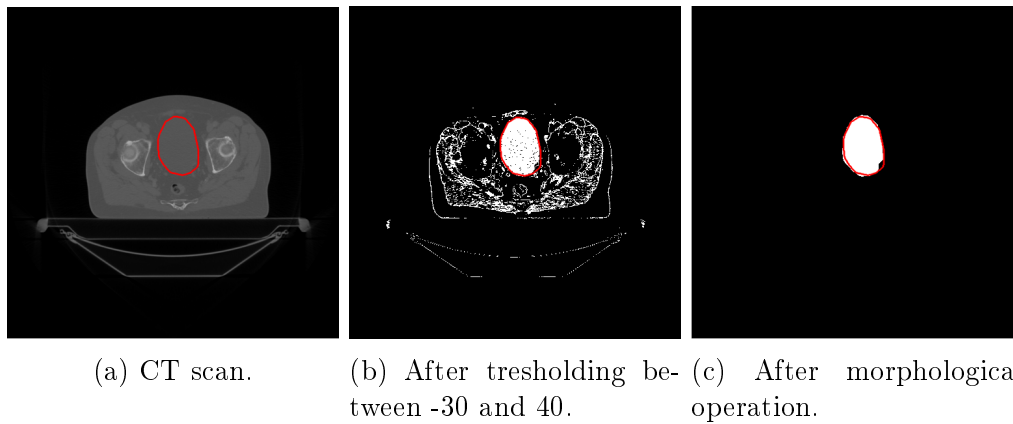


Figure 4.17: Step by step example of extraction of the bladder by thresholding and morphological operation. In red we can see the contour of the bladder delineated by an expert.

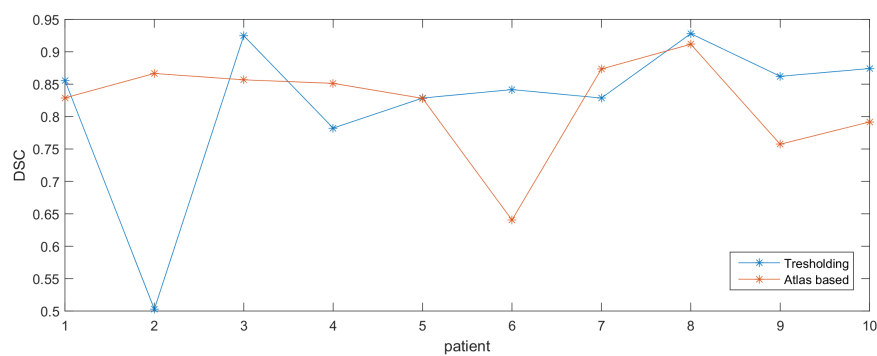
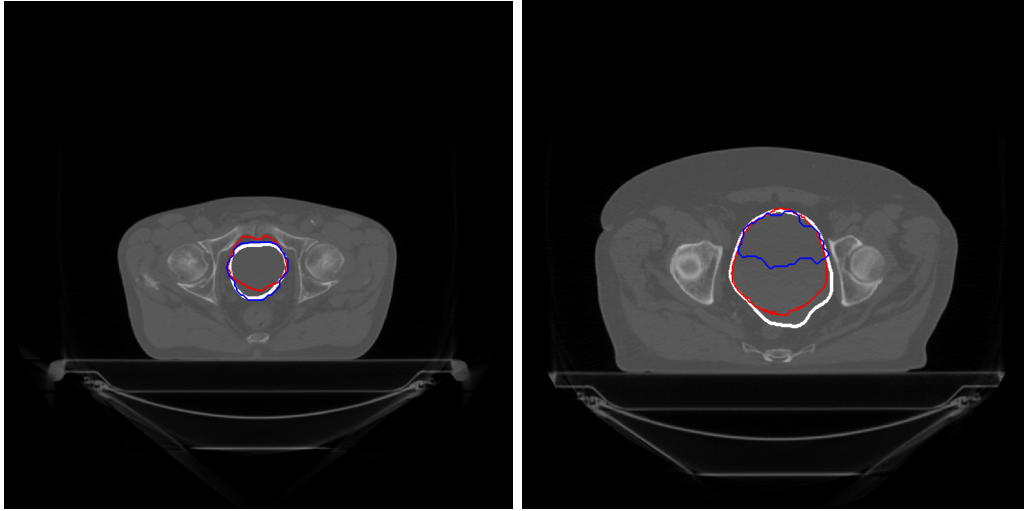


Figure 4.18: Comparison of thresholding and morphological operation in blue and of atlas based method in red.



(a) On patient 6 where thresholding is better than atlas method. (b) On patient 2 where thresholding is worse than atlas method.

Figure 4.19: Visual comparison of the two methods. In white we have the real contour, in red the atlas based method and in blue the thresholding method.

4.4 Robustness to CBCT

As we have seen before, one of the main goals of automatic segmentation is to help an algorithm or a physician to know if the treatment still fits the original planning or has to be re-planned. In this context, the segmentation will be done on images that are taken just after or during each fraction. These images can be CT scans but often they will be images that were taken into the treatment room with other devices such as CBCT. Unfortunately, the quality of CBCT images is much worse than the quality of CT images especially in soft tissues. The difference between the two modalities can be seen in Figure 4.20.

Knowing this difference we will try our algorithm on the CBCT images. The concept is the same but this time the query image is going to be the CBCT image instead of the CT image.

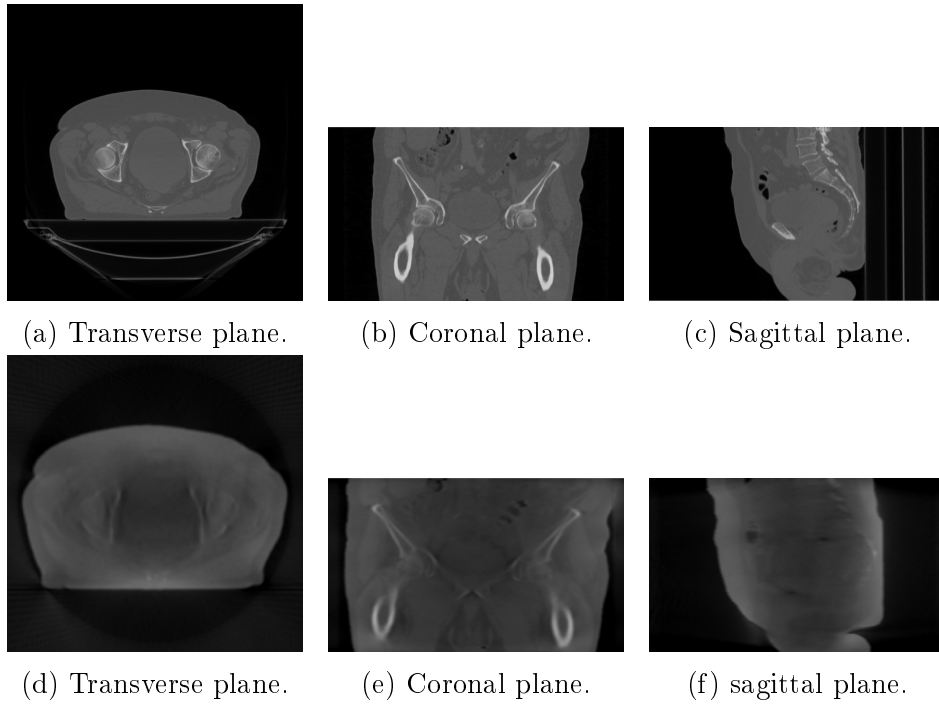


Figure 4.20: Comparison between CT (a,b,c) and simulated CBCT (d,e,f) of the same patient.

We simulate the CBCT image thanks to the CBCT package for OpenReggui (using RTK) ⁵. This tool simulates the projection and the reconstruction and takes into account the three main sources of artifacts in CBCT image [36]:

- The noise: it corresponds to the photon-count noise and it is supposed to follow a Poisson distribution but it is approximated by a Gaussian noise modulated according to the intensity of the signal received on the flat panel as described in equation 4.2.
- The scattering: it corresponds to photons that are deviated of their original path while interacting with matter. These diffracted photons can be detected at the wrong location. Reggui uses a scatter kernel superposition method [37] to take into account the scattering.
- Beam hardening: The photons with low energy in a multi-energy beam may undergo absorption when passing through matter. It can even be absorbed in the material if it is a dense material with high atomic

⁵<https://www.openreggui.org/>

number such as metal. this leads to errors in the recorded data behind highly absorbing material and these errors cause dark streaks in the 3D reconstruction. In Reggui, the beam hardening and its correction is simulated by multiplying the intensity by a factor.

Finally we find the contours in the CBCT by projection and reconstruction of the mask of these contours in the CT.

The following simulation parameters have been used:

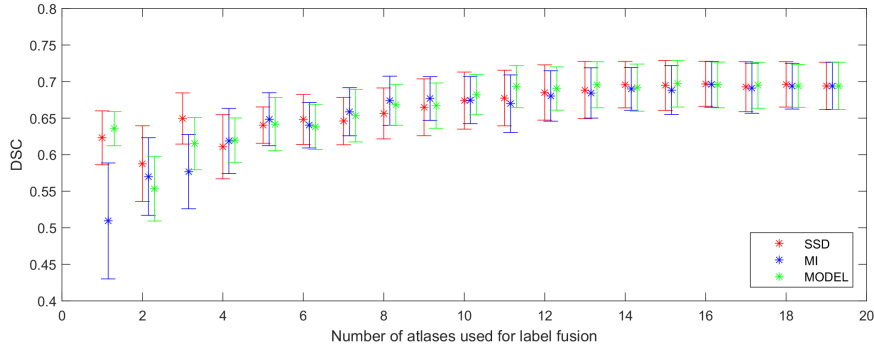
- Source detector distance (sdd) = 1500 mm.
- Source isocenter distance (sid) = 1000 mm.
- Arc angle = 360°.
- Number of projections = 200.
- Projection size (x,y) = (256,256).
- Projection pixel spacing = 2.5 mm.
- CBCT size = (450,350,450) where 350 is the number of slices and 450 the number of pixels in every slice.
- CBCT pixel spacing = (1,1,1) mm.

The default parameters of the CBCT package for OpenReggui have been kept for the scatter and the beam hardening artifact simulation. The noise factor is set to 0.35 (default parameter is 0.75) in the following expression

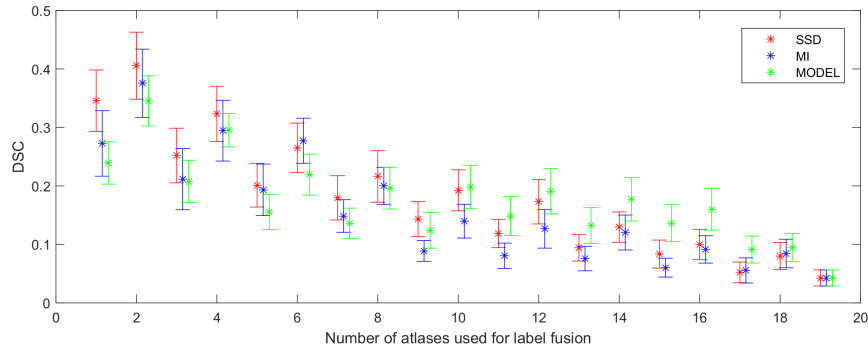
$$I_C + factor * randn(size(I_C)). * sqrt(I_C) \quad (4.2)$$

Where I_C is the intensity of the signal received on the flat panel.

In order to have the best result on our CBCT images we will compare the different ranking methods as well as the number of atlases needed to achieve the best result on CBCT. We can see on Figure 4.21 that for the bladder the DSC slowly increases and reaches his maximum with the model method and 15 atlases with a mean DSC of 0.6971. On the other hand the rectum already reaches its maximum with two atlases and the SSD method. After that it decreases really fast.



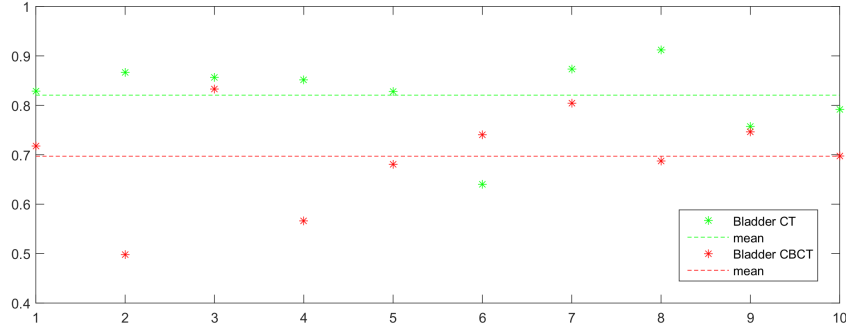
(a) For the bladder



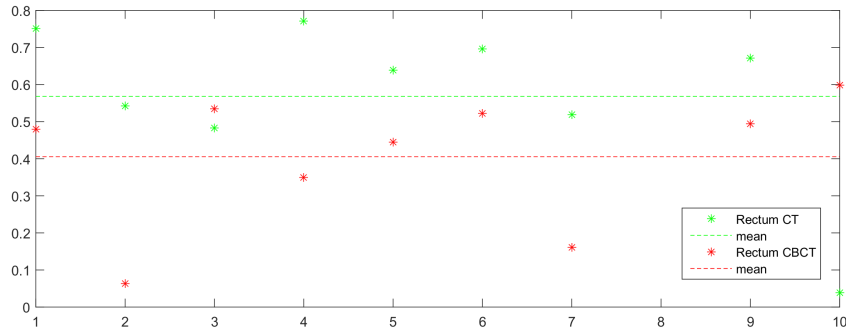
(b) For the rectum

Figure 4.21: Comparison of different ranking methods and number of atlases to select for CBCT images. The * represents the mean over the 10 patients and the bar represents the error on the mean.

Now that we have selected the best method for CT and CBCT images we can compare the DSC given on CT and on CBCT for each patient. The results are visible in Figure 4.22. We can see that in both cases the results given on the CBCT are less good than those on CT. We lose 13% on the DSC for the bladder and 16% for the rectum. Note that in CBCT images the thresholding method to segment the bladder is clearly outperform by the atlas-based method. Indeed the thresholding method gives a mean DSC lower than 10%. This shows the strength of atlas-based method in this kind of images.



(a) For the bladder



(b) For the rectum

Figure 4.22: Comparison of the DSC on CT and on CBCT images for each patient.

Finally we can take a look at one slice of one patient in CT and CBCT and compare how the algorithm works. This is visible on Figure 4.23.

It would have been interesting to have the treatment plan for a patient and to compare the appearance of the DVH according to the type of delineation that is used (automate or manual). If the automate delineation give satisfactory result to two DVH would look alike. In this case the difference in DVH would be only due to anatomical changes and it could then be used to give an idea at the physicians about the need for a re-planning or not. On the contrary if errors on the automate delineation implies difference on the DVH, we can not say if the differences between the DVH are due to changes in anatomy or if it is due to errors caused by the algorithm. In this case it can not give any clues to the physicians.

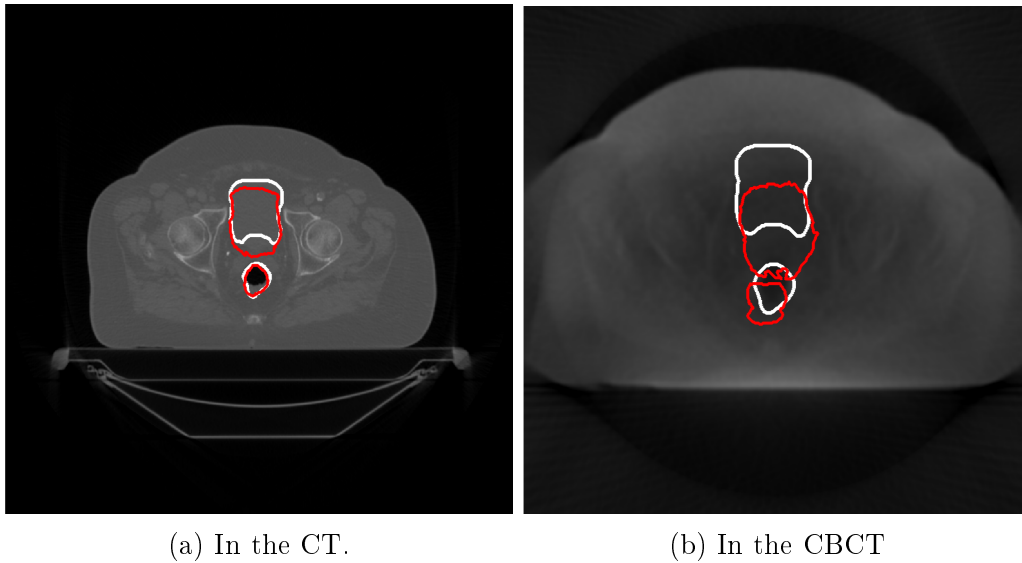


Figure 4.23: Visual comparison of our method on CT and CBCT. The contours found by our algorithm are in red and real contours are in white.

4.5 Source of errors in registration

In this section we will discuss what can occur during the algorithm that leads to errors:

- Presence of **artifact** in the images. This is quite visible if we look at Figure 4.24c compares to the other images of Figure 4.24.
- **Large change in anatomy** between images. This is one of the main problems in the pelvic region. Indeed the bladder and the rectum can take many different shapes and sizes. We can clearly see a difference in the rectum between Figure 4.24d where the rectum is a large black hole and the Figures 4.24a and 4.24b. Differences are also visible in the shape of the bladder between all the images.
- The choice of the **parameters for the registration** can lead to error. A simple example is the use of SSD metric if we have different modalities.
- **Poor contrast** between tissues: We can see for example in Figure 4.24e that it is difficult to spot the frontier between the bladder and other soft tissues.

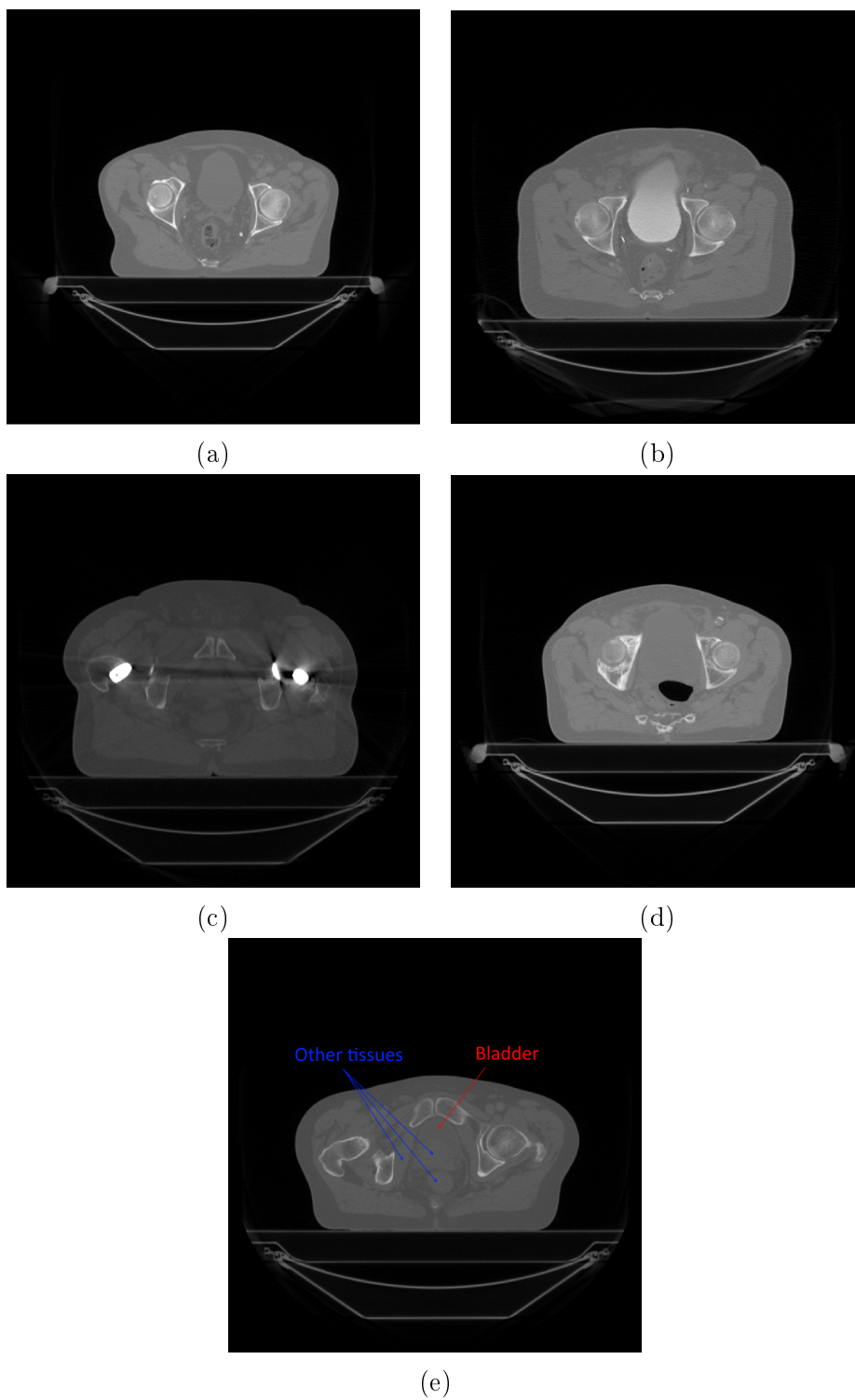


Figure 4.24: Example of error sources in registration.

4.6 Summary

In this chapter we saw the general method used for this thesis and we compared different choices of parameters for the registration, several methods for the atlas selection and methods for label fusion. We compared the results given by each of these methods with the contour drawn by expert on each patient. Our best methods give us dice similarity coefficient around 80% for the bladder and around 60% for the rectum. The main causes of error are large anatomical differences between the patients. Indeed we try to delineate two organs of the pelvic region, the bladder and the rectum and both can have large variations in shape and/or grey-level from one patient to another. The bladder, however, gives better results because of its larger size, the registration will be more focused around it. On the other hand, the rectum is smaller and does not always have the same grey-level leading to error in the registration. Finally we tested our methods on CBCT images in order to use our method for adaptive radiotherapy. Unfortunately the results were worse with CBCT images due to the bad quality of these images.

Chapter 5

Conclusion

In the last 20 years, many improvements have been made to improve the precision and quality of radiotherapy treatment. We have seen the apparition of proton therapy that will deliver the dose locally at the tumor level. We also gain in precision thanks to methods which allow us to modulate the intensity of the beam to create irregular-shaped radiation doses conforming to the tumor whilst simultaneously avoiding critical organs. Better patient positioning during the treatment can also be achieved, thereby avoiding small errors in positioning that can lead to irradiation of wrong areas. In this context, it is more and more important to have a precise localization of the tumor and OARs during the planning phase. Unfortunately, the delineation of such areas in 3D images remains a very time consuming task for physicians. Moreover, efforts are currently made to use adaptive radiotherapy treatment in order to overcome errors in the plan due to anatomical changes that can occur during the weeks of treatment and lead to irradiation of wrong areas. Once again in ART, the delineation of tumor and OARs is very important to give indications to the physicians about the need for re-planning or not but still remains time consuming.

In this context, the goal of this master thesis was to attempt to automate the delineation of organs in the pelvic region thanks to multi-atlas registration. This method uses pairwise registration of atlases with a target image followed by a combination of the transforms labels to provide a segmentation in the target image. In this work, we compared the use of two metrics in the registration steps. We also compared several strategies for atlas selection after rigid registration in order to improve the execution time of our algorithm and to increase the precision of the result. Finally, we evaluated different methods for label fusion. We did this for two organs, the bladder and the rectum, that can have large variations with different sizes, shapes and color

according to the patient. We tried our methods on CT images used during the planning phase and on CBCT images that are in-room imaging used for ART.

From there we concluded that a mutual information metric in the registration leads to the best result. Concerning the atlas ranking, we have to use different methods according to the organs with which we work. For the bladder the best results are achieved by comparing atlases and target images with mutual information and by using 13 atlases. For the rectum it is better to use three atlases and a sum of squares difference as comparator. Concerning the label fusion methods, we conclude that no major improvements are being made while we use weighted methods and that a majority voting method is sufficient. On CBCT images our algorithm gives better results with a model approach for atlases selection for the bladder and still a SSD approach for the rectum, but gives less good results at the end than on CT images.

Because of the large computation time of our current method, we did not have the time to test other registration methods such as non-parametric methods. In the future, it could be interesting to try methods such as Demons or Morphons registration that are non-parametric methods and that seem to outperform parametric methods according to some papers [28]. They are also supposed to be faster. We have also seen that we could have better results with a better choice in the selection of our atlas. We should therefore try to find new selection methods, that should lead to better results. We could try to make the selection after non-rigid registration to win in precision but it requires an acceleration of the registration algorithms. Moreover, we currently work with 20 atlases in a region with large variability. If we work with a large number of atlases, we would be more likely to find atlases that look like the target image. But on the other hand, a large number of atlases would require a clustering step, to avoid having to register each of the atlases on the target image.

Finally we can conclude that atlas-based methods have some difficulties to find precise contours in regions with large variability, but that we can explore some tracks in order to improve them and gain in precision. With some improvements and with the arrival of new technologies to improve image quality of in-room imaging, we hope that these methods can help physicians to improve the quality and precision of radiotherapy thanks to automatic adaptive radiotherapy.

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Appendix A

Image used as atlas and target image



Figure A.1: Patient 1.



Figure A.2: Patient 2.



Figure A.3: Patient 3.

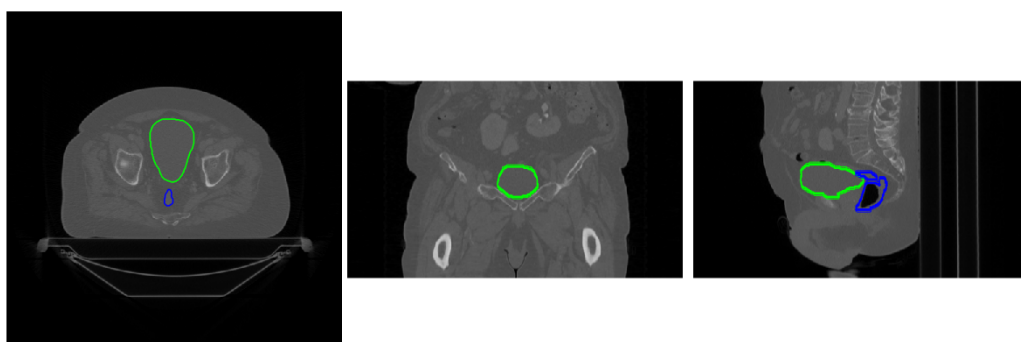


Figure A.4: Patient 4.

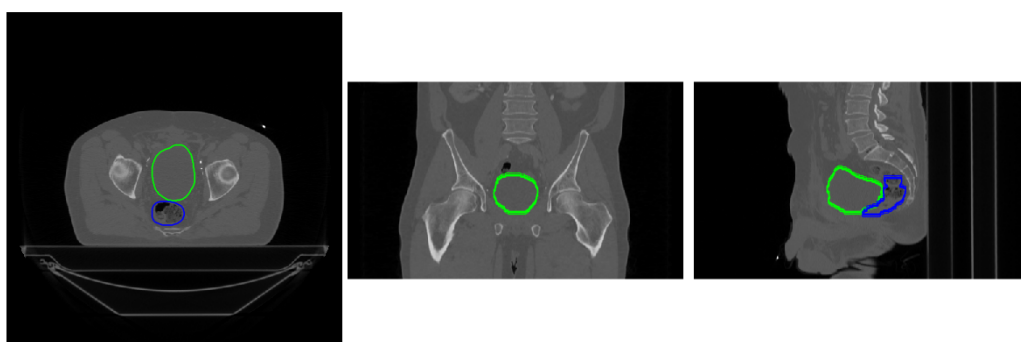


Figure A.5: Patient 5.

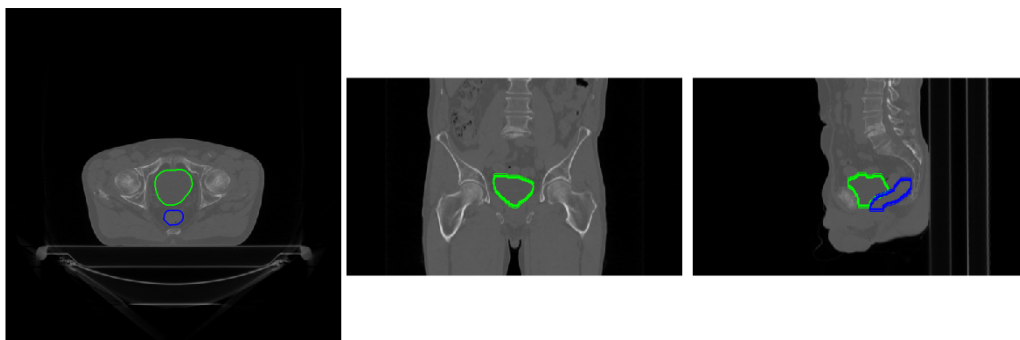


Figure A.6: Patient 6.

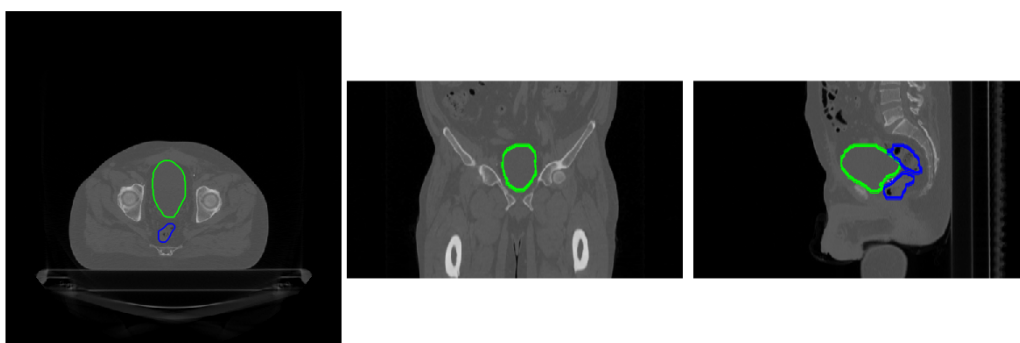


Figure A.7: Patient 7.



Figure A.8: Patient 8.

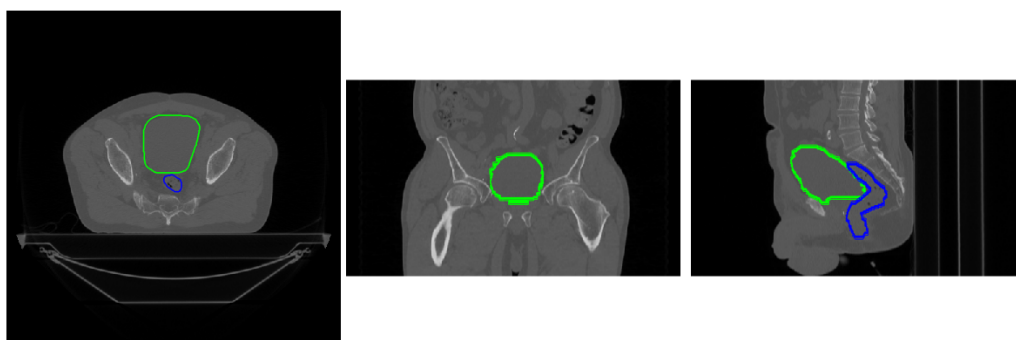


Figure A.9: Patient 9.



Figure A.10: Patient 10.

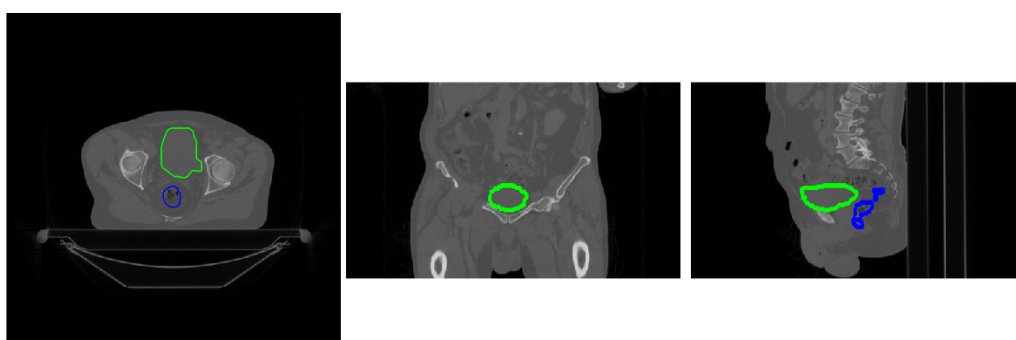


Figure A.11: Patient 11.

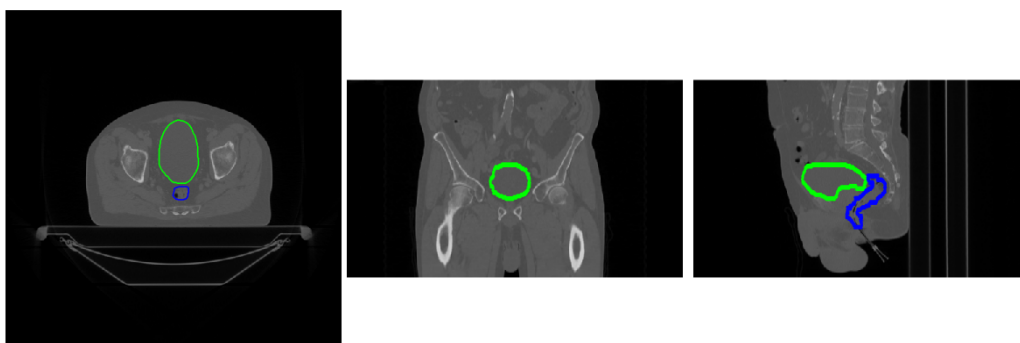


Figure A.12: Patient 12.

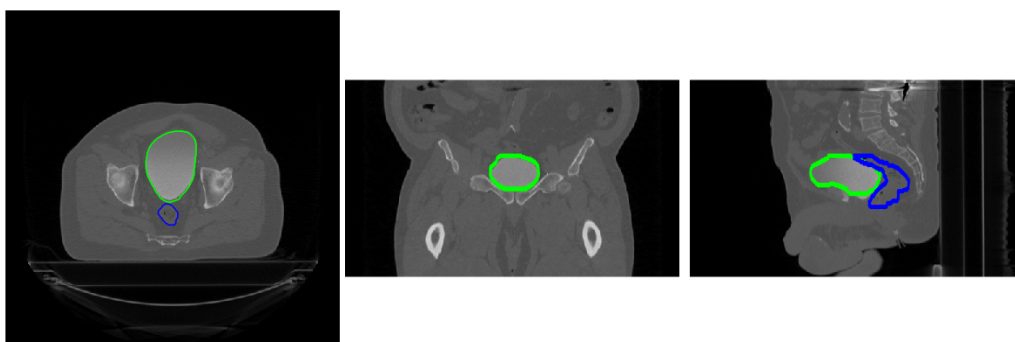


Figure A.13: Patient 13.



Figure A.14: Patient 14.

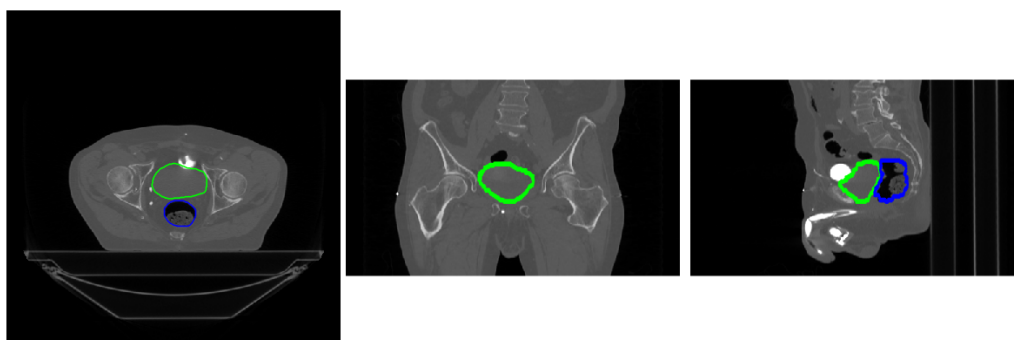


Figure A.15: Patient 15.

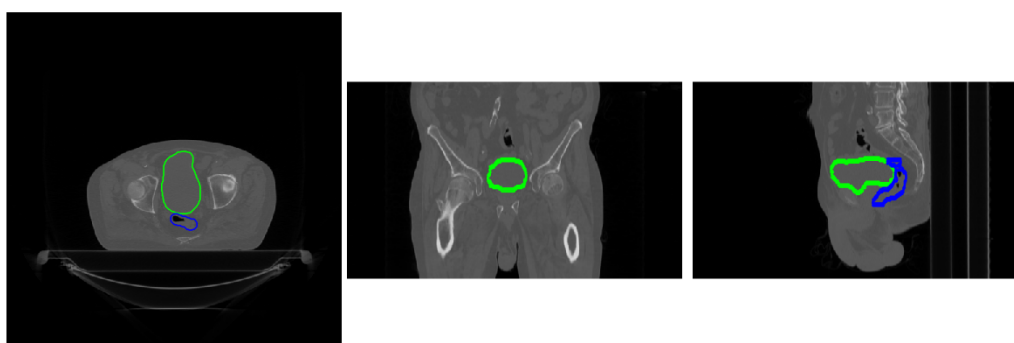


Figure A.16: Patient 16.



Figure A.17: Patient 17.

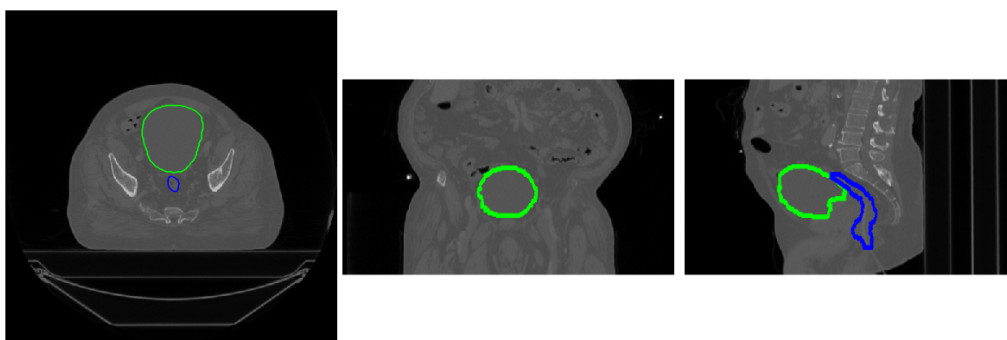


Figure A.18: Patient 18.

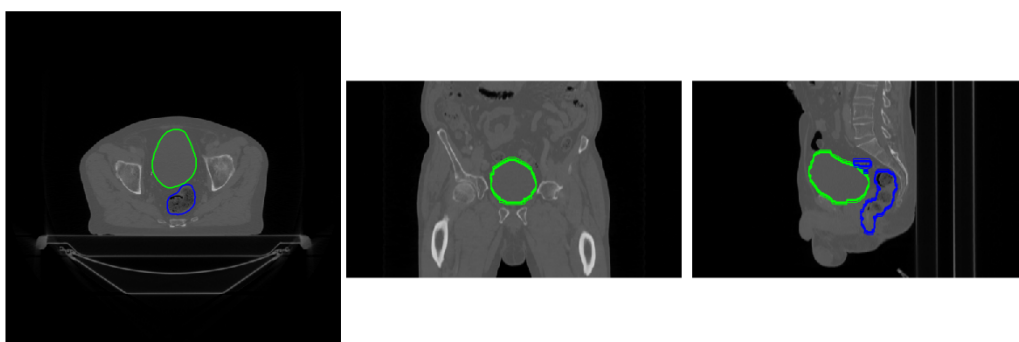


Figure A.19: Patient 19.

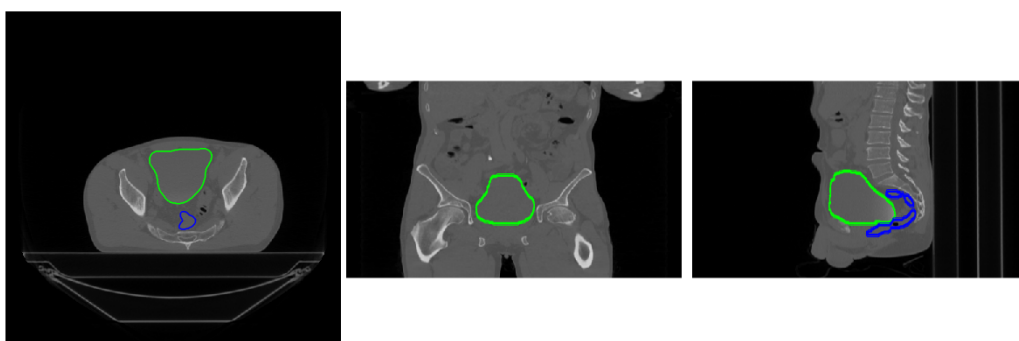


Figure A.20: Patient 20.

