

Non-rigid deformation of treatment plans for on-line adaptive protontherapy

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Abstract

External radiotherapy is a major component of cancer treatment. Its objective is to deliver a high measure of radiation to tumors while minimizing the dose inflicted to healthy tissues. Protons have the ability to deliver a peak of energy (the "Bragg peak") in a precise location depending on the atomic composition and densities of the tissues in their path, making them highly suitable for radiotherapy. Because the anatomy of the patient is continuously changing during the course of the treatment that may last more than 30 days, the position of the Bragg peak is subject to uncertainties, which may have dramatic consequences for the patient. The goal of this master thesis is to tune the treatment to day-to-day anatomical changes by performing the so-called "adaptive planning". We submit an original strategy where the treatment plan, optimized before the start of the treatment and approved by a radiation oncologist, is adjusted to the new anatomy. Three test cases have been designed: 1) anatomical changes around a tumor with unmodified position and shape; 2) tumor displacement; and 3) tumor reduction. The evaluation of a plan is conducted by analysing the dose volume histogram of the predicted dose by a Monte Carlo algorithm. Except for the tumor reduction, our adapted plans manage to produce a dose close to the desired one. In conclusion, non-rigid deformation of treatment plan could be used in addition of other method to perform efficient adaptive protontherapy.

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List of Abbreviations

BP(s)	Bragg Peak(s)
BeV	Beam Eye View
CT	Computed Tomography
CTV	Clinical Target Volume
DVH	Dose Volume Histogram
GTV	Gross Tumor Volume
Gy	Gray
ICRU	International Commission on Radiation Units & Measurements
OAR(s)	Organ(s) At Risk
PBS	Pencil Beam Scanning
PTV	Planning Target Volume
RTV	Raw Target Volume
SPR	Stopping Power Ratio
TP	Treatment Planning
WEPL	Water Equivalent Path Length

Chapter 1

Introduction

Several strategies exist to treat cancer. The main ones are chemotherapy, surgery and radiotherapy. The last method aims at hitting a targeted area with ionizing radiations to damage the DNA of cancerous cells. The cancerous cells being less efficient at repairing their DNA than healthy cells, it is possible to deliver lethal doses of radiation to tumors while maintaining an acceptable toxicity to healthy tissues. In this way, cancerous cells accumulate sub-lethal damages and ultimately die while healthy tissues can survive, but not without suffering from radiation. Hence, the aim of radiation therapy is to deliver a high enough dose to the tumor while keeping it as low as possible in healthy tissues. The unit used to monitor the dose received by an area is the Gray (Gy), with one Gy representing energy accumulation in joules per kilogram.

Among all the delivery radiation systems some of them are internal to the patient, placing a radiating source in the nearest region possible to the tumor, while the others are external and categorized as external beam radiation therapy, the latter being the chosen modality in more than 75% of radiotherapy treatments. The photon source is usually fixed on a gantry allowing to choose freely the beam orientation, an important feature since the superposition of differently-oriented beams makes it possible to decrease the dose received by healthy tissues, or even to avoid vital organs. The external radiating beam is generally composed of X-rays (photons), propelled toward their target with a high energy, typically 0.5 to 25 MeV and which leave radiation on their path. This beam is shaped by a collimator, commonly made of tungsten, to obtain a radiation conform to the targeted area.

Opposed to photons are the protons, which leave most of their dose in a limited area called the bragg peak (BP). By regulating the energy

of the protons, the dose can be delivered to a very specific area and thus a high sparing of healthy tissues can be achieved. Protontherapy can involve different delivery systems, and this master thesis will focus on pencil beam scanning (PBS) where the beam is decomposed in independent beamlets shot separately, sweeping the target. The superposition of different Bragg peaks enables the delivery of a constant dose inside of the whole target.

Once the type of therapy is chosen, the next step is to create a treatment plan. The treatment plan contains all the information about the different settings of the therapy and beam delivery and use CT-scans as a snapshot of the patient. Planning is a delicate operation as we want a plan which maximizes the chances to kill cancerous cells, proportional to the dose received by the tumor, and minimizes complication probabilities, correlated with the dose delivered to healthy tissues. This problem is quite difficult to solve, and compromises must be made. As planning complexity is also increased with the high number of parameters, especially in PBS (number and direction of beams, number and position of beamlets for each beam, beamlet energies and weights, ...), it is almost impossible to perform this process manually and it requires automated computation. The most used strategy, called inverse planning, is to set prescribed doses to the tumor and healthy tissues and use them as objectives to perform an optimization. Physicians must compulsorily accept and validate the plan before the treatment start.

But the treatment plan optimization shows one particular drawback: The plan works very well for the specific situation it has been optimized for, but can not adapt to changes. Therapy treatments against cancer are often spread over weeks and accompanied by weight losses or anatomical changes. Those changes can take the form of a tumor displacement, or the movement of an obstacle in (or out) the beam's route. If they are too large they distort the dose, which can have terrible results like tumor under-dose or irradiation of healthy tissues. This last point is particularly prejudicial if the tissues in question are qualified as "organ at risks" (OARs). OARs are important organs that often feature a higher sensitivity to irradiation and should therefore be spared as much as possible.

In adaptive planning, the plan is regularly updated in order to take the anatomical changes into account and limit their negative effects

on the treatment. Traditionally, this method requires to completely re-compute the plan, and the new plan must be approved by physicians, time consuming steps leading in a disruption of clinical workflow. The main goal of this thesis is to study the feasibility of using the original treatment plan to speed up the creation of the new one. It is the first step of a project aiming to implement an adaptive planning strategy able to adjust the plan in a few minutes so that the physician's approval would also apply to the new, adapted plan. The strategy is to use image processing to compute the anatomical changes going over the tumor and then apply them to the plan and verify that the dose distribution to the tumor and OARs is as close as possible to the original one. The new plan performances are obtained by simulating its dose distribution with a Monte Carlo algorithm.

Chapter 2 reviews the state of the art, containing more information about radiotherapy, protontherapy and treatment planning, it also details our objective. Finally, it ends by listing and explaining the different tools used for this work. Chapter 4 explains how we modeled the different types of anatomical changes and the algorithms created to adapt the plan. Chapter 5 contains our results, which are discussed here as well. Finally, Chapter 6 concludes this master thesis.

Chapter 2

State of the art

This chapter begins by a brief reminder about cancer, what it is and that are the three most common treatments, with more explications about radiotherapy. Then we detail protontherapy and its advantages compared to traditional radiotherapy. Finally, we talk about adaptive planning, explaining briefly how it is done, why it can be improved and how we will tackle this problem.

2.1 Cancer

Cancer is the name given to several diseases causing an abnormal growth of tissues, called tumor, which can endanger its host's life. The cancer type will depend on the type of cells it affects, e.g., carcinoma for cancers affecting epithelial cells, or sarcoma for cancers affecting bone tissues. Because one cancerous cell can grow an entire tumor, we can never be sure that a cancer is totally treated and will never come back. Thus an cancer is never cured but only in remission state, meaning that symptoms have disappeared.

Most often, patients undergo different treatments at the same time to maximize remission probability. Cancers are categorized by their location, their type and their extent. The prescribed treatment depends on the cancer category and is chosen by physicians. We will talk here about surgery and chemotherapy, while section 2.2 will detail radiotherapy.

Surgery is often the first option, as it has relatively few side-effect in comparison with other treatment modalities ([1]). It is mostly used to treat local cancers and it removes a tumor, partially or not, but it can also be used to diminish symptoms like the pain provoked by the tissue growth.

Chemotherapy is the use of drugs to kill fast growing cells or reduce

their multiplying rate. More than 100 exist, each one having its own effects and side-effects. They can either be used independently or in combination and can work in different ways, but all intervene in cells replication cycle, meaning that they especially affect fast growing tissues like tumors, but also healthy cells like those growing hair by example. They can directly damage DNA, or interfere with enzymes and proteins used in the replication cycle. For more information, the American Cancer Society lists 7 chemo-drug categories, and details how they work ([2]). Each category regroups drugs that use the same means to treat cancer. Some belong in more than one group.

The Belgian Cancer Registry estimates that, on the 31st of December 2013, 3% of Belgian population had been diagnosed with cancer since 2004 ([3]). For the year 2013, they registered 65.487 new cases of cancer in Belgium, and expect this number to reach 78.000 in 2025. But at the same time, medicine and science's progress make cancer less and less deadly. They established that the risk of succumbing to cancer diminishes by 1.6% per year for men, and 0.5% for women.

2.2 Radiotherapy

Radiotherapy is the use of ionizing radiations, typically photons, to treat cancers. It can have a source internal to the patient, for brachytherapy, or not. In this case, it is called external beam radiotherapy. Brachytherapy typically represents 20% of radiotherapy treatment and is used when the tumor is relatively small and localized with great precision ([4] - see chapter 13). It improves the dose localization in such cases. As for other treatments, different modalities exist. The source can be inserted in body cavities near the tumor or incorporated to the tumor itself through surgery. The source can either be removed after having delivered the prescribed dose, or left in place until complete decay. The dose emitted by the source is not measured in Gy but in Gy per hour, and follows standards edicted by the International Commission on Radiation Units & Measurements (ICRU). Low dose rate brachytherapy emits between 0.4 and 2 Gy per hour while high dose rate brachytherapy emits more than 12 Gy per hour.

When brachytherapy is not available, physicians resort to external

beam radiotherapy. The source is then fixed on a gantry able to rotate and deliver beams in several direction, while the patient lies still on a horizontal table.

The dose deposition of photons, shown on figure 2.4 page 10, fea-



FIGURE 2.1: Illustration of external beam radiotherapy. The radiation source is fixed on a gantry able to rotate around the patient to produce beams in various directions. Source: [5]

tures a linear-exponential decrease with depth after a rapid rise in the few first centimeters. Thus, tissues are irradiated significantly upstream and downstream the tumor. To avoid high dose delivery to healthy tissues, a single treatment can use different beams oriented in different direction. The figure 2.2 shows the dose distribution obtained by a plan combining 2 different beams.

As external beam radiotherapy uses high precision tools to irradiate a restricted area from different directions, a treatment plan must be written. ICRU reports define and describe volumes usually used by practitioners for this operation ([7],[8]). The gross tumor volume, GTV, is the volume of the tumor visible by medical imaging, typically CT scans. As some cancerous cells can be detached from the main tumor, a safety margin is added around the GTV to enlarge it in what is called the clinical target volume (CTV). A second margin is added to form the internal target volume (ITV), which takes organ motion into account. Finally, the planning target volume (PVT) includes one or possibly several ITV, depending on the number of tumors. Margins can be added to this last volumes to takes uncertainties in dose

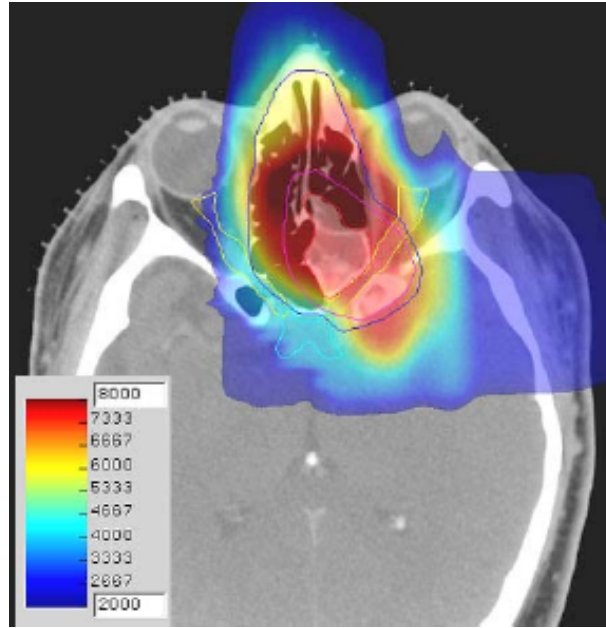


FIGURE 2.2: Illustration of the use of multiple beams in radiotherapy. To avoid high dose delivery in healthy tissues, the treatment has been divided in 2 beams. Source :[6]

distribution into account.

The goal of treatment planning is thus to maximize the dose in the PTV while minimizing it outside the PTV. As there is a high number of parameters influencing the dose distribution, an optimizer is used to perform the planning and a physicians must validate the plan.

2.3 Protontherapy

This master thesis is focused on protontherapy, an external beam radiotherapy using protons, which have a different behavior than photons. Contrary to photons, protons show a slowly increasing deposition along their path with a sharp and high concentration of energy deposition at the end of its range . This effect is called the Bragg peak (BP). The range of the proton is proportional to its energy and depends on the stopping power of the material it must go through, the stopping power being the rate at which charged particles lose energy with the distance traveled in matter.

Because of their physical properties, protons deposit almost no dose

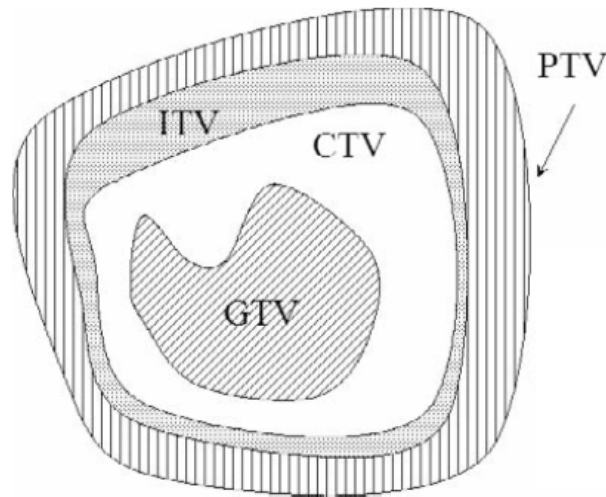


FIGURE 2.3: Representation of the different target volumes used in radiotherapy. The GTV is the volume occupied by the tumor, the CTV is the GTV enlarged to take into account possibly undetected cancerous cells, the ITV takes physiological movements into account and the PTV is the volume used by the treatment planning. Source : [4]

downstream the tumor and a reduced dose upstream, resulting in a strong decrease of the dose received by healthy tissues compared to conventional radiotherapy. It is possible to deliver an homogeneous dose across the tumor by combining the dose distributions of protons of various energies, leading to the so-called "Spread-Out Bragg Peak" ([9]).

In the last years, several planning studies have shown that protontherapy has significant advantages against classic radiotherapy, inducing the capacity to reduce the dose in healthy tissues while being as effective for tumor treatment ([11]-[17]). Some also suggest a decrease in the late effects of the therapy ([18], [19]). The figure 2.5 represents the dose distribution of protontherapy (left) and classic radiotherapy (middle) as well as the differential between the two (right). We can see that protontherapy deliver less dose to healthy tissues.

However, protontherapy suffers from drawbacks and its main advantage, a high concentration of dose at the end of its range, is also its greatest weakness. Indeed, uncertainties in the treatment workflow may significantly affect the accuracy of the range: imaging of the patient, stopping power computation, dose calculation, patient

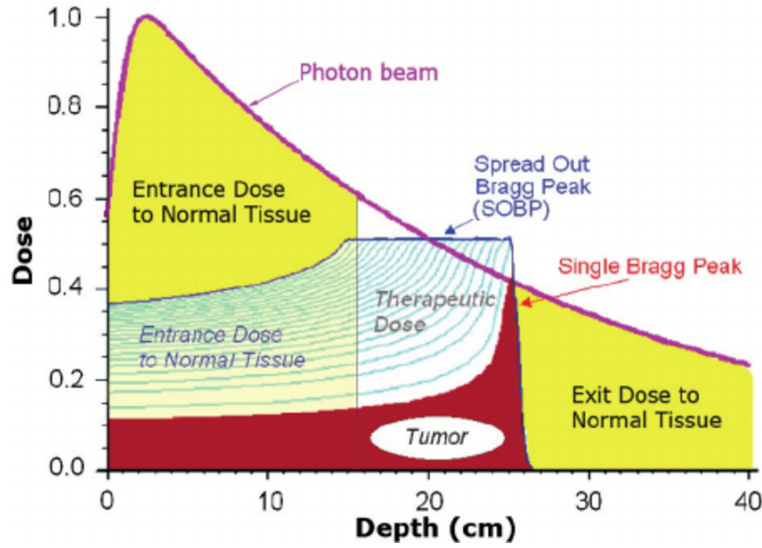


FIGURE 2.4: Dose distribution of X-rays versus of single energy protons and a spread-out Bragg peak (SOBP). Source: [10]

set up, etc. Those uncertainties are typically managed by adding proportionally-increasing safety margins to the PTV.

As stated earlier, this master thesis will focus on pencil beam scanning (PBS). The principle of this method is to produce a small spot that is magnetically steered. After a determined duration, the beam is switched off and moved to the next spot, performing a scanning of the plan perpendicular to the beam. The energy is also changed to cover the tumor in depth. Because energy switching takes more time than magnetic steering, spots are often regrouped per energy, in so-called "layers". In a homogeneous and cubic media, protons from the same energy layer will have the same range. But, due to density variation in the human body, the different spots of a same layer will generally not be in a plane ([9] - see chapter 11).

The biggest drawback of PBS is the increase of the planning system complexity. Indeed it is needed to choose position and weight (the duration of beam activation) of each spot and to obtain a well distributed high dose in the tumor and a sufficiently low dose outside of it. This is not problematic during the creation of the patient first treatment plan. But, as we will see in the following section, this original plan can be inappropriate for future fractions of the treatment and must be adapted. When that happens, the complexity of the treatment planning extends the computation time and delays the beam

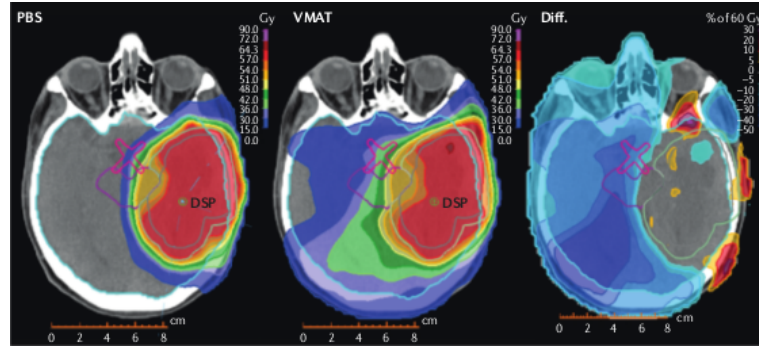


FIGURE 2.5: Comparison of dose distribution obtained with different treatments for the same case. Left : Proton radiotherapy (PBS). Middle: Intensity-Modulated Radiation Therapy (IMRT). Right: Visualization of differential dose. Source: [20]

delivery, which greatly perturbs the treatment system workflow.

2.4 The problem: tumor motion and adaptive planning

As we have seen, protontherapy generates a dose distribution with a steep gradient, which limits the irradiation of healthy tissues and OAR. Unfortunately the SOBP profile is highly sensitive to the BP spatial configuration, which means that the slightest change in their position can distort the dose distribution and render it non uniform or lead to OAR irradiation([21]-[23]). Such problems are tackled by adaptive planning, i.e. the computation of new plans during the treatment([21], [24]).

Though adaptive planning works, it takes time. In 2015, Sahaja Acharya et al ([25]) obtained an average of 26 minutes to perform recontouring, reoptimization and quality assurance of 52 adaptive treatment plans. Moreover as the adaptive planning creates a whole new plan, the physician's approval is needed. An alternative would be to implement a new adaptive planning method creating an adapted plan from the modification of the original one. By keeping as much information from the original plan as possible, we aim not only to minimize computation time, but also to obtain a new plan similar enough to the original one that the physician approval could apply to both. .

In the specific case of proton therapy with pencil beam scanning, we propose a new methodology based on two distinct steps. First the position and energy of each spot are adapted to cover the displaced tumor. The second step would be the adaptation of the different spot weights to obtain a uniform dose distribution in the form of a fast constrained optimization. This master thesis will concentrate on the first step, and try to prepare the different spots weights and position in order to have a good basis for optimization and to reduce the second step's duration. For now the goal is not to compute working plans, but to design an adaptive algorithm based on non-rigid deformation and assess its performances in order to ascertain the relevance of the method.

In this chapter we began by a global reminder concerning cancer and the most common treatment used today, then focused on radiotherapy. After a brief view of brachytherapy, we gave more details about the external beam therapy and explained how physicians determine which volume will undergo radiations. The next step was to introduce protontherapy, explain its advantages against classic radiotherapy, as well as its drawbacks. Finally, we described adaptive planning, explained why the current state is problematic and exposed the goal of this master thesis.

Chapter 3

The tools.

This chapter lists which tools were used to handle, build and evaluate treatment plans in this master thesis, and how. Most of those tools are in-house software from the MIRO department of UCL or developed for the ImagX project, a partnership between UCL and IBA.

3.1 CT-RTSTRUCT

As mentioned in previous chapters, cancer treatment needs a visual representation of the tumor and its surrounding, not only to visualize and characterize the tumor, but also to plan the treatment. This is done by using CT-scans.

CT scans are 3D image of the patient and are generally saved in the DICOM format, a standard in medical imaging. One DICOM file represents one CT slice, and is typically constituted of $512 * 512$ pixels. In this master thesis, each CT-scan is constituted of 201 slices of $55*55$ cm separated by 2mm from each other. Thus, the superposition of those slices creates voxels of $1.17*1.17*2$ mm. In MATLAB, the scan will be modeled as a $256*256*201$ tensor. Each element of the tensor represents the linear attenuation coefficient of the corresponding voxel, expressed in Hounsfield unit (HU).

RTStruct are DICOM files containing all of the information about the positions of the different target volumes and organs at risk.

In this master thesis, those files were created using RayStation, a software developed by RaySearch Laboratories AB, based at Stockholm, Sweden; and imported into matlab thanks to the IMREviewer software created by John Lee.

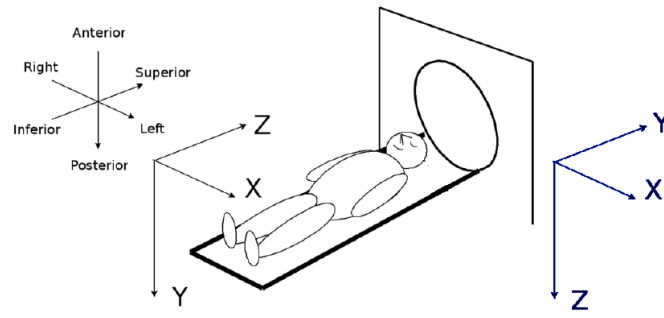


Figure 2. DICOM coordinate system.

FIGURE 3.1: Representation of CT (in black) and BeV (in blue) coordinates systems with respect to the patient orientation for an horizontal couch and a gantry angle of 0° .

3.1.1 A word on patient positioning and coordinates systems.

A coordinate system is necessary to handle CT scans and link them to the physical space in which the patient and the treatment equipment evolve. The axes of the CT coordinate system are represented in black on the figure 3.1. The X axis is parallel to the patient left-right axis, the Y axis to the anterior-posterior and the Z axis to the inferior-superior. One CT slice is a cross section along the X and Y axis. When treated, a patient lies on his back on a rotating table and the source, fixed on a gantry, will rotate around him to deliver the beam oriented with a certain angle called the gantry angle. A gantry angle of zero means that the beam is parallel to the Y DICOM axis; i.e anterior to posterior direction. The coordinates of the planning system are called Beam Eye View because the Z axis is parallel to the beam. We will specify each time Y_{BeV} or Z_{BeV} , to distinguish between this and the X;Y;Z DICOM. The Y axis is parallel to the patient inferior-superior axis. A modification of the X coordinate also represents a left-right displacement, but this time it is perpendicular to the beam. On the figure 3.1, the BeV coordinate system is represented in blue for a gantry angle of 0° and an horizontal couch. Where CT origin is fixed, the BeV origin can be computed anywhere in the CT slice.

3.2 MIROpt

MIROpt is a Mixed Robust Optimizer for proton pencil beam scanning currently developed by Ana María Barragán Montero, and is used to build treatment plans. By using matlab and IPOPT software (open source Interior Point OPTimizer for large scale non-linear problems), MIROpt can perform a regular optimization or a robust one taking into account the systematic and random set-up errors, but also proton range error. The optimization method is a almost-Newton one, called the limited-memory BFGS Hessian approximation¹.

In the context of this paper, MIROpt has been used to build the original treatment plans, and all functions developed to adapt the plan were based on it.

MIROpt requires a set of inputs: the gantry angle, the CT-scan as well as the contour of the tumor and OARs with their respective prescribed dose. The user can also provide the center of the BeV coordinate systems, if not specified, the isocenter will be set at the geometric center of the tumor.

The very first thing done by MIROpt is the conversion of the HU units of the CT in a stopping power ratio (SPR). The SPR of a material is the ratio of its stopping power compared to the stopping power of the water and is registered in a conversion-table accessible to MIROpt. It allows MIROpt to express the pathway crossed by the protons in water equivalent path length (WEPL), through raytracing: at first, MIROpt calculates at what distance the protons crossed in each voxel and then multiplies these distances by the SPR of the corresponding voxels.

The next step is to compute the positions and the energy layers. The volume where to place the spot, called the RTV, is obtained by expanding the initial target volume with a margin predefined by the user. The depth of each spot is calculated so that the space between layers, determined by user, will be the same for all of them and so that the whole RTV will be covered.

¹for more information about this method, see:
<https://rtmath.net/help/html/9ba786fe-9b40-47fb-a64c-c3a492812581.htm>

Once the spots are placed, MIROpt uses IPOPT to perform an optimization of all spot weights. For this optimization, different objective functions are used. For the treatment plan created in this work, a min/max function was chosen:

$$Total_{Cost} = Cost_{min} + Cost_{max} \quad (3.1)$$

$$Cost_{max} = \frac{1}{N_{ROI}} \sum_{k \in ROI} (d_k - D_{max})^2 \cdot H(d_k - D_{max}) \quad (3.2)$$

$$Cost_{min} = \frac{1}{N_{ROI}} \sum_{k \in ROI} (D_{min} - d_k)^2 \cdot H(D_{min} - d_k) \quad (3.3)$$

$$\text{With } H(x) = \begin{cases} 1 & \text{if } x \geq 0 \\ 0 & \text{if } x < 0 \end{cases}$$

In equations 3.1 to 3.3, N_{ROI} is the number of voxels in the region of interest (ROI), d_k the computed dose at the current iteration for voxel k while D_{min} and D_{max} are the values for dose prescription (in Gy). The computation of these objective functions requires the evaluation of the dose d_k for each ROI at each step. MIROpt does it by computing P , a 2D matrix where the dose for all beamlets is stored so that each column corresponds to a spot and each row to a voxel in the CT, and multiplying it by the vector of weights. Hence $d_k = P_{jk} * w_j$, where w_j is the weight for the j th spot and P_{jk} the dose for voxel k of spot j .

MIROpt outputs text files containing all of the information about the treatment plan including the total number of fractions, the beams directions, the isocenter for each beam (origin of the BeV coordinate system), expressed in millimeters, the number of layers and, for each layer, its energy (in MeV) with the (X_{BeV}, Y_{BeV}) position (in millimeters) of each spot and their respective weight. An example is given in appendix A for a very simple plan with only two layers and 2 spots per layer.

3.3 MCSquare

The dose distribution corresponding to a treatment plan is traditionally computed analytically by projecting the range of the protons, adapted to WEPL, in the patient without taking inhomogeneities into account. As this technique cannot model all interactions between protons and the patient, it leads to range uncertainties. A Monte Carlo method is the process of simulating a great number of individuals, typically several millions, with characteristics picked at random in order to perform a statistical simulation method. In 2012 Paganetti ([26]) compared the use of Monte Carlo algorithm and analytic methods to compute the dose distribution. He established that Monte Carlo algorithms can reduce range uncertainties from 4.6% of the total range + 1.2mm to 2.4%+1.2mm, mainly by reducing the impact of local lateral inhomogeneity.

Nevertheless, Monte Carlo algorithms need to simulate a great number of protons to be statistically relevant and thus suffer from a long computational time which lowers their practical use. MCSquare (many-core Monte Carlo) is a MC simulator especially designed to tackle this problem ([27]). As can be guessed from its name, MCSquare uses the multi-core architecture of recent CPU to reduce the computational time of dose distribution simulation. Optimized for Intel Xeon Phi CPU, it is able to simulate the dose distribution of 10^7 protons in approximately 25 seconds in optimal configuration. The appendix B shows why it is important to simulate such a number of protons.

Although it is not its original goal MCSquare was used in this master thesis to evaluate the performance of treatment plans as it outputs, among other things, a map of the dose from the inferior-superior axis point of view (see figure 3.2, left), and a cumulative DVH. DVH stands for dose volume histogram and is commonly used to assess the treatment quality. It represents how much of a target, expressed in percentage, is covered by a certain dose. It begins at 100%, as it is impossible to receive a negative dose, and gradually goes down to 0% once the maximum dose is passed (see figure 3.2, right). An ideal DVH for a target would be an horizontal line at 100% descending vertically to 0% at the prescribed dose, meaning that the whole target receives enough dose without any area being over-dosed. For

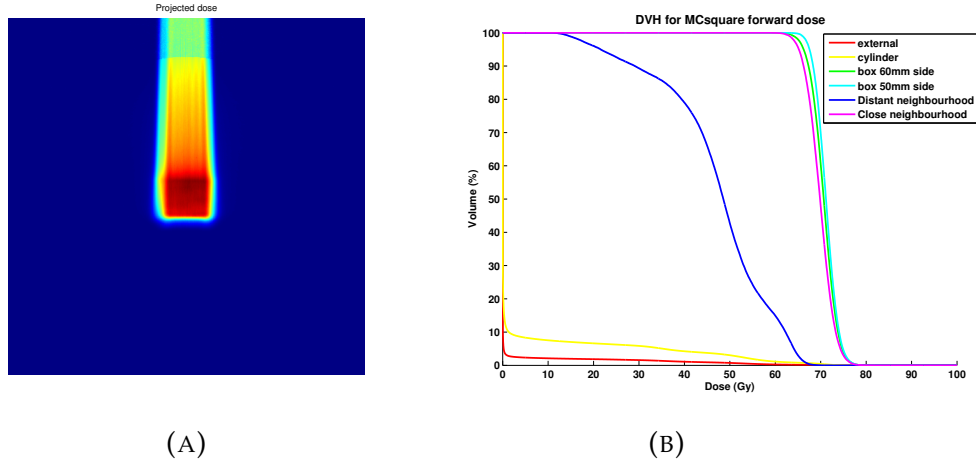


FIGURE 3.2: MC square outputs. (A) Dose distribution map for a plan targeting a cube centered in the CTs. (B) DVH. Each curve represent the volume (in %) of a target exposed to a certain dose.

further explanation of performance assessment through dose map and DVH, see section 5.1.

3.4 REGGUI

The REGGUI image processing software developed by Guillaume Janssens is able to perform image registration, filtering, segmentation and application specific to radiotherapy, as CBCT reconstruction and DVH. It was used to visualize the CT used to compute the original plan (the moving image), the new CT (the fixed image) and to perform non-rigid registration between them in order to adapt the plan. The resulting deformation was then used on the original spots to create a new plan. The deformation field was computed with the Morphon algorithm. This algorithm uses a multiresolution approach to compute the deformation field between two images by using the local phase of each image and a certainty matrix C . At each resolution, the algorithm performs several iterations to update the deformation field and C in order to maximize the certainty over the whole deformed image. An article from Plumet et al [28], shows an implementation and a brief overview of this algorithm, and Wrangsj et al [29] provided a full detailed description about the subject. For this research, the deformation fields were computed using 8 different

levels of resolution, with 10 iterations per scale. The solid regularization was done using normalized Gaussian with a standard deviation of 1.5 pixels.

Chapter 4

Development

In this chapter, we first explain how the problem will be taken on and divided in three sub-problems, then we describe how we proceed to solve each of those sub-problems. The first two will be tackled with the same algorithm, which moves the beamlets positions, and the last problem, tumor contraction, will require some linear regression to tune the beamlet weights.

4.1 A phantom approximation of the human body

As explained in Chapter 2.4, physiological changes in the patient's body can lead to a displacement and/or a deformation of the tumor and OARs. Thanks to the CT scans and image processing software Reggui, it is possible to compute a deformation field that maps each element of the original CT scan to the place it occupies in the new one. This deformation can be separated in two independent components: rigid and non-rigid deformation. As rigid deformation is itself the combination of a translation and a rotation, those two aspects will be used independently. On the other hand, non-rigid deformation is a complex problem with various potential forms, and only one of them, size reduction, will be studied here.

Two virtual phantoms were built to simulate a human body and a tumor within it. For each of the two, all objects were modeled by volumes of water. The first phantom consists of a sphere of 15mm radius, which will be the target, and a cube with 32.22cm edges, which will play the role of the body. The deformation applied to this phantom is the rotation of the external cube around the tumor. This deformation modifies the quantity of matter crossed by the protons and models

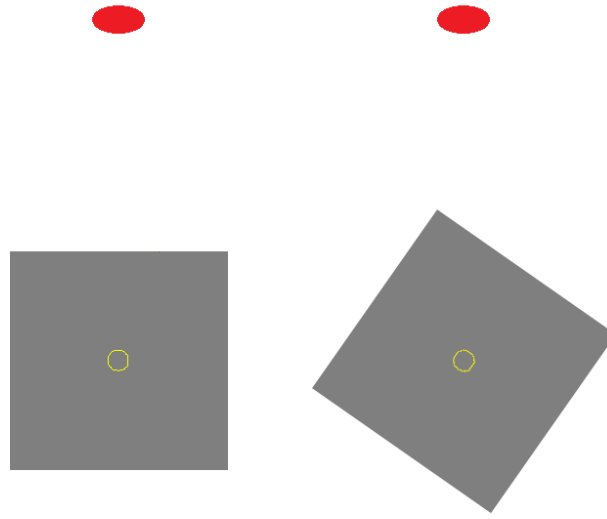


FIGURE 4.1: Axial cross-section of the first phantom. The target is a sphere of water (yellow circle) centered in a cube of water. The proton source is represented in red. Left : Reference case. Right : After a rotation of 35° .

anatomical changes occurring around the tumor. The original plan will be optimized to deliver a dose of 60Gy to the target.

The second phantom will be used to analyze both the translation and volume reduction of the tumor. In this case, the target is a cube and the body is represented by a cylinder with a 42.96cm radius. For the translation case, a cube with 3cm edges originally positioned at the center of the cylinder will be displaced of 4 and 8 cm perpendicularly to the beam. A translation parallel to the beam is uninteresting because it would only cause a modification of the layer energies, as the depth of a spot only affects its energy. As for the first case, the prescribed target dose is 60Gy.

For the volume reduction case, a cube with 6cm-long sides, also positioned at the cylinder center, will be transformed into a cube with 5cm edges centered at the same position. In this case, the prescribed dose is 70Gy.

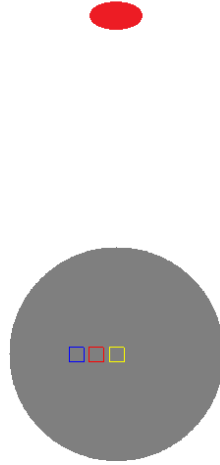


FIGURE 4.2: Axial cross-section of the second phantom. The target is a cube with 3cm edges at the center of the cylinder for the reference case (yellow). It is then translated 4cm (red) and 8cm (blue) to the left.

4.2 Phantom rotation and tumor rigid translation

The cases of the first two types of deformation will be treated with the same strategy, where the beamlets position and energy are changed, but the spot weights stay the same as in the original plan. Section 4.2.1 describe the first strategy we considered to tackle the problem and explain why it does not work, while the section 4.2.2 explain the final strategy. The result will be presented in the section 5.2.

4.2.1 A layer-based approach

As we have seen in the background section, the treatment plan is organized in layers of beamlets with the same energy, creating a grid of targeted Bragg peaks distributed in the target volume. As the form of the target has not changed at all, a simple approach to adapt the plan to the modification applied to the target would be to align the center of the plan to the center of the target and adjust the energy of each layer in order for the protons to reach the right depth, and thus the tumor. Figure 4.3 shows the corresponding work-flow: the system inputs are the CT scans corresponding to the pre-treatment (CT scan 1) and the new ones (CT scan 2). While the first CT scans are used to build the original plan via MIROpt, the latest are used

to align the beam with the new tumor position and compute new energy layers. The algorithm to choose the new energies is the same used in MIROpt: the energy range required to reach the farthest and nearest positions of the tumor in WEPL are computed and sampled with n equally distant energies, where n is the number of layers in the original plan. The plan is then updated with these new energies and positions, and the dose is computed by MC2. Figure 4.4 shows the dose distribution map obtained with this technique: even if the target is indeed reached by the majority of the protons, the dose shape is distorted and does not fit the target anymore. The cause for this is that beamlets with the same energy are not neighbors in space, but in WEPL. And even if the tumor form does not change, the WEPL variation of each beamlet can be modified drastically. In fact, the WEPL can change even when the tumor is not modified at all: if an obstacle (e.g., a bone) moves between the radiation source and the target hiding it partially, the protons passing through this obstacle will have to travel a greater WEPL than before while the others will not be affected by the changes.

4.2.2 A beamlet-based approach

A solution to this problem is to adapt the energy of each beamlet separately, deconstructing the layer-structure of the plan. Because of heterogeneities, this method will significantly increase the number of different energy layers in the treatment plan, and a post-processing will be needed to optimize treatment delivery time. But as the goal of this master thesis is simply to gauge the feasibility of this technique, step has not yet been explored.

Some additional operations are needed for the plan deconstruction in beamlets. Indeed, the only information we have about beamlet is their trajectory (a starting point, BeV Coordinates, and a direction) and energy. The BP exact position is not stored in the plan, and must then be recalculated.

The first step will be to retrieve information. This is will done with the energy and beamlets BeV coordinates and by performing a reverse raytracing. In order to do it we will need more information, the CT scans used to design the original plan, which will be used to compute the SPR along a certain path. Indeed, even if we don't know

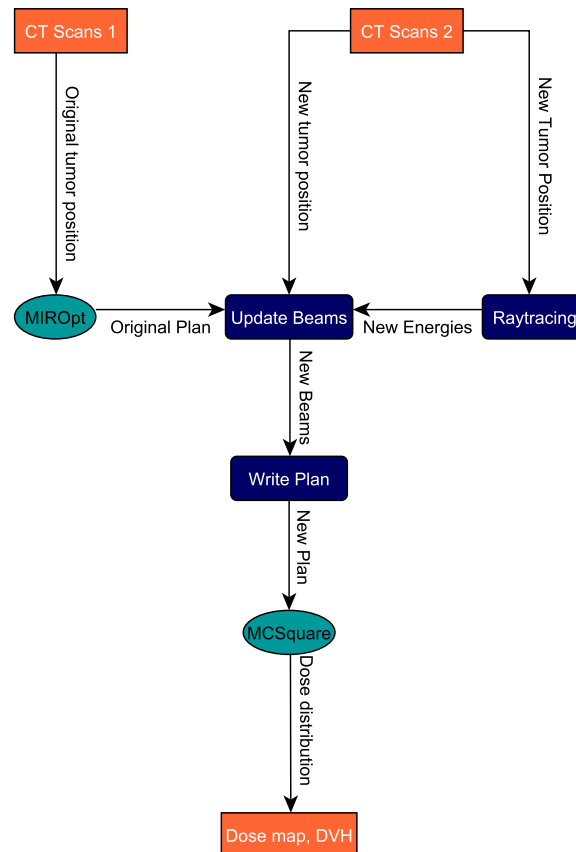


FIGURE 4.3: Work flow of the layer-based approach. Inputs : Two sets of CT scans. Output : A dose map and a DVH to evaluate the new plan performances. MIROpt is used to build the original plan from a first set of CT scans. The second set of CT-scans is used to update the tumor position and the energy of the new beamlets. A function is especially designed to write a new plan and test it with MCSquare.

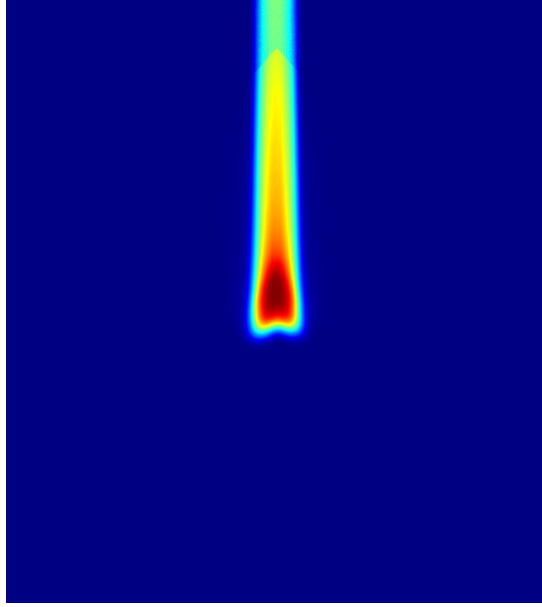


FIGURE 4.4: Example of dose map obtained by the layer-based approach. The target is a 15mm radius sphere in the center of a cube. Even if the target is recovered, the dose distribution loses its sphericity.

exactly where the destination of the beamlet is, the BeV coordinates and the Gantry Angle allow us to know the trajectory of the protons. On the other hand, the beamlet energy and the SPR of each voxel will provide the distance between the proton source and the desired BP.

The first operation is to bring all beamlets with the same X_{BeV} and Y_{BeV} coordinates together and to process only one raytracing corresponding to the deepest point belonging to both the beamlet trajectory and the CT-scan. Once we know the evolution of the WEPL along the proton path, we can convert it into energy and find the depth corresponding to the different levels of beamlet energy beamlet energies. Secondly the tumor deformation and displacement are computed with Reggui and applied to each beamlet position. The beam source is also displaced to be aligned with the new isocenter of the tumor. A raytracing is then performed to update the energy of each beamlet separately, and the new beams are encoded in a new plan.

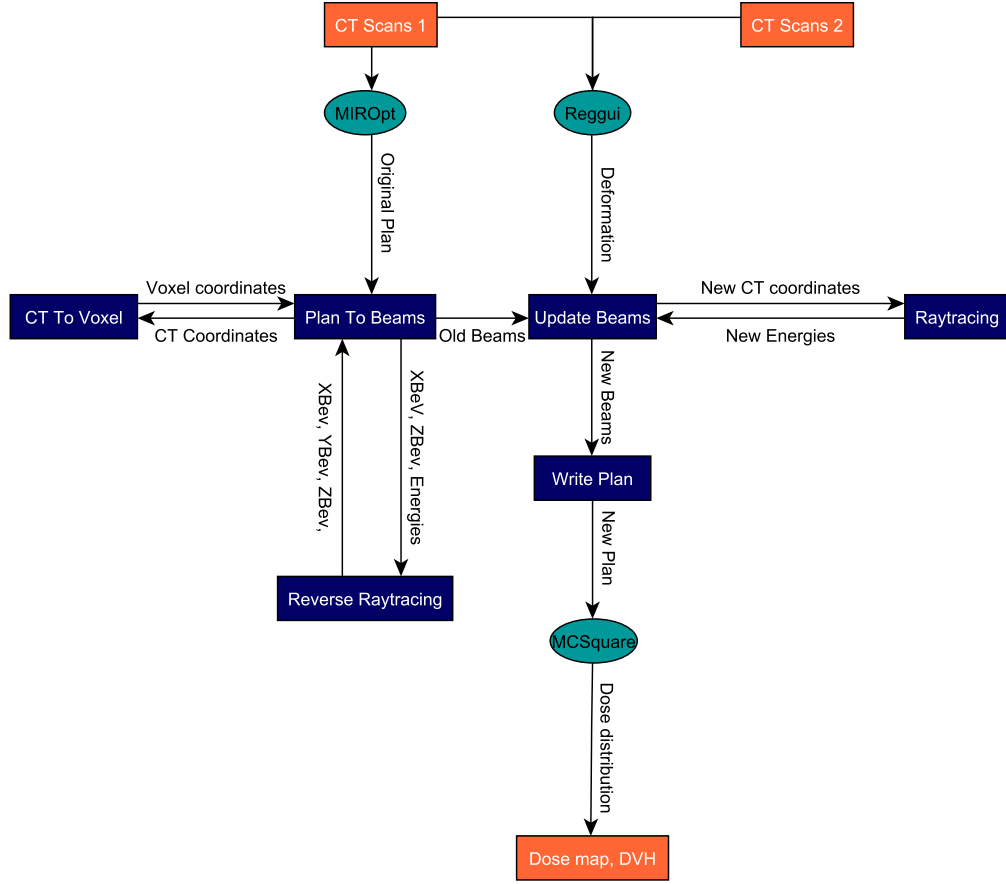


FIGURE 4.5: Work flow of the beamlet-based approach. Inputs : Two sets of CT scans. Output : A dose map and a DVH to evaluate the new plan performances.

MIROpt is used to build the original plan from a first set of CT scans, while Reggui computes the deformation between the two sets of CT scans. The next step is to retrieve all of the information about the beams, and requires a reverse raytracing to find back all BP positions, as well as a function to convert coordinates between the different systems (CT to Voxels). Raytracing is used to update each beamlet energy. A function is especially designed to write the new plan and test it with MCSquare.

4.3 Tumor contraction

Tumor reduction cases are more difficult to deal with than the previous kind: to adapt the plan, we must move the BPs in the new tumor volume. We must change our strategy and adapt it to this difference. Section 4.3.1 further describes the consequences and specificity of non-rigidity while section 4.3.2 touches on the solutions first implemented and briefly details their results, relying solely on MC-Square outputs appearance. Section 4.3.3 lists some corrections as well as the definitive solutions that we found. The final results will be detailed in section 5.3.

4.3.1 A new approach: beamlet interpolation

The BPs displacement in a volume included in the original one means that, if we do not change the different spot weights, the same number of protons will be delivered in a smaller area and, inevitably, the dose received by the tumor will be increased. Moreover, non-rigidity implies that each BP will be subjected to a translation different from the other, leading to non-uniformity of the dose distribution.

The solution developed here relies on working with two different sets of beamlets :

- Original beamlets, as they are encoded in the original plan. They will not be used directly, except to compute the two other sets.
- Deformed beamlets t , with weights w whose position has been updated with the non-rigid deformation obtained from Reggui.
- New beamlets x , in the same position as the original ones, but with modified weights s to interpolate those of deformed beamlets.

The strategy is not to move the original beamlets to their new positions, but to create new beamlets that interpolate from the deformed ones' initial positions. Two functions were built as an answer and are described in the next section, as well as a brief dose distribution analysis. Updated versions of those functions are described in section 4.3.3.

4.3.2 Linear regression of beamlets weights: prototype

As our final objective is to compute a fast adaptive algorithm, the first regression method implemented is a interpolation based on closeness. The weight of each new beamlet is updated through the following operations:

1. Finding the deformed beamlets t in a set perimeter around the current new beamlet x_i and refer to them as winners.
2. Updating s_i , the weight of x_i by a linear regression of the winners' weight w . Let d_{ij} be the distance between x_i and t_j :

$$s_i = \sum_j \frac{\frac{1}{d_{ij}}}{\sum_k \frac{1}{d_{ik}}} w_j \quad (4.1)$$

The figure 4.6 shows an example of the weighting method, while the figure 4.7 shows the dose map obtained by MCSquare when testing the resulting plan. As we can see, the dose is non-uniform and only 80% of the volume receives a dose superior to 40Gy. The reasons of this poor performance are explored in section 4.3.3.

The second method that we implemented relies on a strategy opposite to the first one: rather than interpolating the deformed beamlets, we can divide them between nearby new beamlets. So, for each deformed beamlet t_i with a spot weight w_i , we process the following operations:

1. Find the new beamlets x , with weights s present in a set perimeter around the current deformed beamlet and refer to them as winners.
2. For each winner x_j , update its weight s_j by adding a portion of w_i to it. Let d_{ij} be the distance between t_i and x_j :

$$s_j = s_j + \frac{\frac{1}{d_{ij}}}{\sum_k \frac{1}{d_{ik}}} w_i \quad (4.2)$$

An example is pictured in Figure 4.8, and the results of the plan computed with this method are on figure 4.9. We can see on the dose

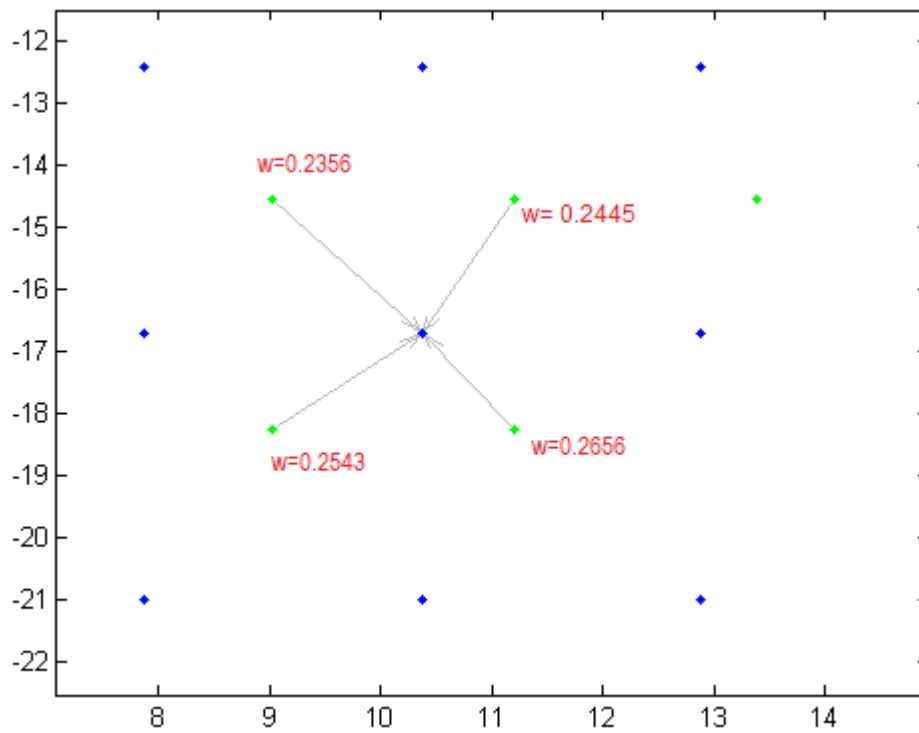


FIGURE 4.6: Example of the first method updating beamlets weights. The blue points are the new beamlets and the green points are the deformed ones. The arrows link the new beamlet being currently updated and the nearest deformed beamlets. The red text represents the multiplying factor in equation 4.1: Nearest neighbors are more important than others.

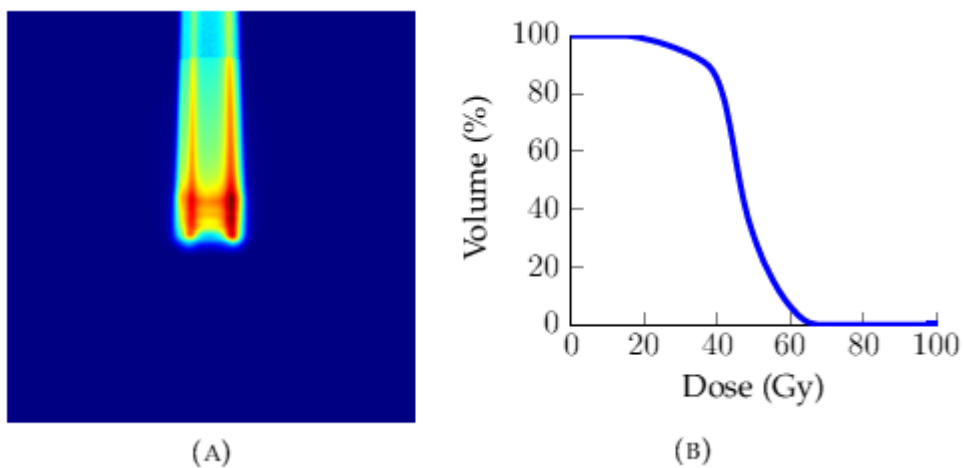


FIGURE 4.7: Results of the first method of adaptive planning for non-rigid deformations. (A) Dose map. (B) DVH.

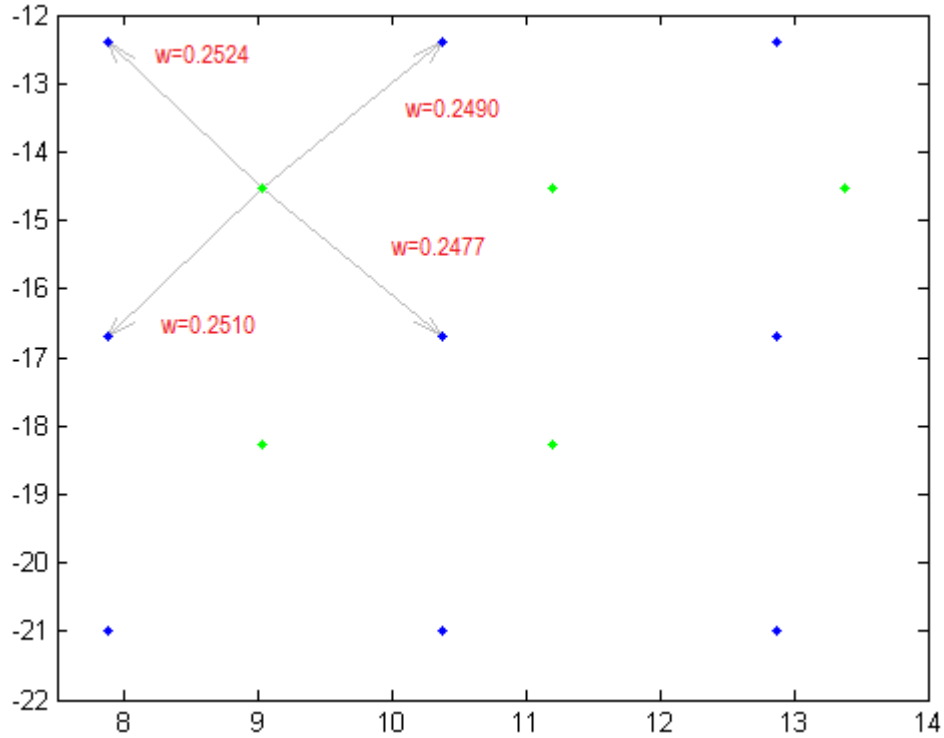


FIGURE 4.8: Example of the second method updating beamlets weights. The blue points are the new beamlets and the green points are the deformed ones. The arrows link the deformed beamlet being currently treated with the nearest new beamlets. The red text represents the multiplying factor in equation 4.2: Nearest neighbors receive more weight.

map that the target center tends to be overdosed compared to the rest, while the DVH shows a maximal dose above 100Gy. This is not acceptable, a diagnosis will also be established in the section 4.3.3.

4.3.3 Linear regression of beamlets weights: Improvements

As stated in the previous section, the dose distribution obtained by the first two methods is not satisfactory, we performed a diagnosis and identified two problems, both of them affecting both methods. The first one is caused by the deformation field, which is not constant nor isotropic. In consequence, some beamlets are never chosen as winners and remain null. As we do not want to expand the search window too much, we modified the algorithms so that when

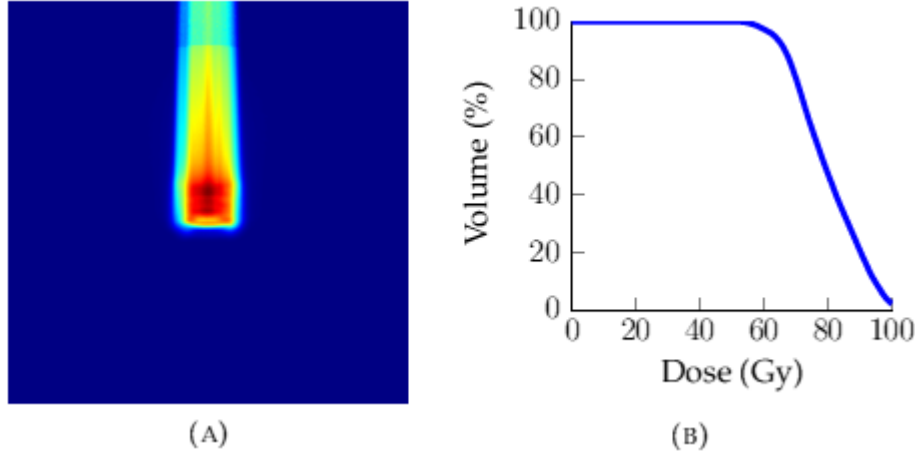


FIGURE 4.9: Results of the second method of adaptive planning for non-rigid deformations. (A) Dose map. (B) DVH.

a beamlet does not pick any winner, and only in those circumstances, it would perform a second search, using an extended window.

The second problem affects the so-called distal layer, which is the layer with the greatest spot weights and the greatest contributor to the dose. In the two methods described above, this layer contribution is greatly reduced by the use of equations 4.1 and 4.2 and the dose distribution is thus altered. In order to solve this problem, we decided to perform the regression only if the difference between the mean using all winner's weights was smaller than 30% of their greatest value. If it is not the case, the concerned weight is updated with the greatest weight among the winners:

Let s_i be the weight of the new beamlet x_i , and $w_{i,1}, \dots, w_{i,N}$ the weights of $y_{i,1}, \dots, y_{i,N}$ the winners corresponding to x_i , i.e. the deformed beamlets which will influence the weight x_i . Let M_i be $\max(w_{i,1}, \dots, w_{i,n})$ and $m_i = \frac{1}{N} \sum_n w_{i,n}$. Then:

$$s_i = \begin{cases} m_i & \text{if } \frac{M_i - m_i}{M_i} \leq 0.7 \\ M_i & \text{if } \frac{M_i - m_i}{M_i} > 0.7 \end{cases} \quad (4.3)$$

As in the previous section, we will describe 2 methods differing from each other by the way they use to find the winners $y_{i,1}, \dots, y_{i,N}$. The first method, called "method one" or "algorithm one" in the rest of this paper, will select the winners for x_i by searching the deformed

beamlets in a set perimeter. If it does not find any winners, it will perform a second search using an extended perimeter, with a doubled radius.

The second method, called "method two" of "algorithm two" from now on, will start with the deformed beamlets. For each deformed beamlet t_i , it searches the new beamlets x in a set perimeter neighborhood of t_i . If it does not find any, it will perform a second search using an extended perimeter, with a doubled radius. t_i is then added to the winners of all x found during the search.

Hence, the aim of the method one is that all x_i find at least one winner, and the one of method two is that every t_i is selected as least one time as a winner.

4.3.4 Additional step: Weight normalization

For both methods described in the previous section, we will try 3 different situations. For the first one, the plan is not modified further and will be referred as the "raw" plan. For the second situation, weights are normalized so that their total sum is the same in the new plan and in the original one:

Let s_i be the weight of the new beamlet x_i , S the cumulative of weight of all new beamlets, e.i. $S = \sum_i s_i$, and W the cumulative of weight of all beamlets in the original plan. We perform:

$$s_i = s_i \cdot \frac{W}{S} \quad (4.4)$$

This normalization will be referred as "global normalization" as it multiplies the weight of all beamlets by the same factor.

As for the last possibility, the beamlets are firstly divided in 4 groups along each dimension (for a total of 4^3 groups, the figure 4.10 shows an example in 2D). Then, they are normalized so that the sum of weights in each group is the same in the new plan and in the original one.

Let s_i be the weight of the new beamlet x_i , J the group which comprise x_i , S_J the cumulative of weight of all new beamlets belonging

to J , e.i. $S_J = \sum_{x_i \in J} s_i$, and W_J the cumulative of weight of all beamlets belonging to J in the original plan. We perform:

$$s_i = s_i \cdot \frac{W_J}{S_J} \quad (4.5)$$

This weight normalization will be referred as "local normalization" as the factor multiplying each beamlet depends on its position in space.

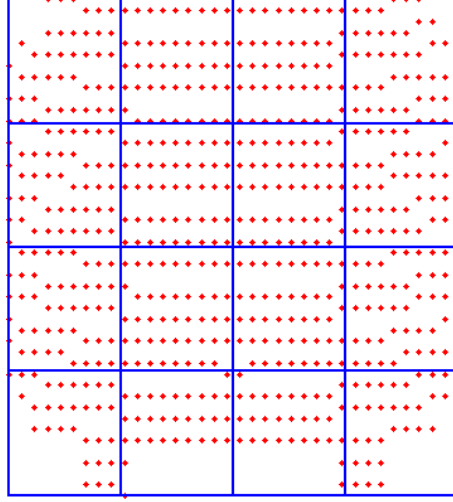


FIGURE 4.10: Separation of the beamlets in 4 groups per dimension: sketch representation in 2D. The beamlets are the red points, and the blue lines represent the delimitations between each group.

In this chapter, we first described how we have divided the problem of tumor deformation in three distinct sub-problems and how we modeled them. Then we focused on the phantom rotation and tumor rigid displacement, explaining why we need to perform the adaptive replanning on each beamlet independently. This is done by computing back the position of each beamlet thanks to the information in the original plan and to adapt them one by one. Finally, we discussed upon the strategy we established to adapt the plan to a tumor volume reduction, beginning with simple regression method and explaining why they do not work. We then finished with more elaborated versions of regression-like algorithms tuned with optional steps.

Chapter 5

Results and discussion

Now that all test cases and algorithms have been described, it is time to show the resulting dose distribution in each situation and to evaluate it. In this chapter, we first explain how MCSquare outputs are used to extract relevant features and assess the treatment plan performance. Then we go through each case, show dose maps and DVH, accompanied by tables with numerical values. These tables will firstly give the results of the reference plan obtained by MCSquare, then the raw results of our algorithms. Each table will be followed by a second one where the doses have been normalized. Finally, we will analyze and discuss the results in this chapter's last section.

5.1 Evaluation of the treatment plan

As stated in section 3.3, we use MCSquare to assess a plan performance. MCSquare outputs two figures: the dose map and the DVH. The dose map is used to judge qualitatively the dose distribution and the DVH allows us to compute statistical features about the dose, such as the volume receiving a particular dose, or the dose perceived by a certain percentage of the volume. We based our statistical features on the ICRU report No. 83, which describe the standards for prescribing, recording, and reporting Intensity-Modulated Photon-Beam Therapy [30]:

- D_{95} the dose absorbed by 95% of the target volume. We want it greater than 95% of the prescribed dose.
- D_{50} the dose absorbed by 50% of the target volume. We want it as close as possible to the prescribed dose.

- D_5 the dose absorbed by 5% the target volume. We want it lower than 105% of the prescribed dose.

Those features were computed on the target volume, which is the equivalent of the CTV in clinical cases. For the tumor contraction, as we compare different algorithms, we will also use the difference between the D_{95} and D_5 , named Gap_{95-5} . It should ideally be null, indicating that we preserve the dose steep gradient, and we will appoint the algorithm which minimize it as our best one for this case.

5.2 Results of the beamlet based approach

In this section, we describe the results for the phantom rotation and tumor rigid translation. For each case, we begin by the results obtained with the reference case, then the results of the different test cases. With a prescribed dose of 60Gy for both cases, results will be judged as satisfactory if D_{95} is above 57Gy and D_5 under 63Gy.

5.2.1 Phantom rotation

The environment used in this case is the first one described in section 4.1, and consist of a spherical target in a cube of water. To test the performances of our algorithm, we created different test case by rotating the cube of 10, 20, 30, 40 and 45°. The figure 5.1 represents the dose map and the DVH for the reference case while figure 5.2 represents the dose map and DVH for rotation of 30°, figures for other angles are in appendix C. The table 5.1 comprises the statistical features for the reference case (0°) and the different test cases. We also reported the number of energy layers in each plan, which all use 878 beamlets.

5.2.2 Tumor translation

The environment used in this case is the first one described in section 4.1, and consist of a cubic target in a cylinder of water. Two test cases were used, a lateral displacement of 4 cm for the first, and of 8cm for the second one. The figure 5.3 represents the dose map and the DVH for the reference case while figure 5.4 represents the dose map and DVH for displacement of 4cm, the figure for displacement of 8cm

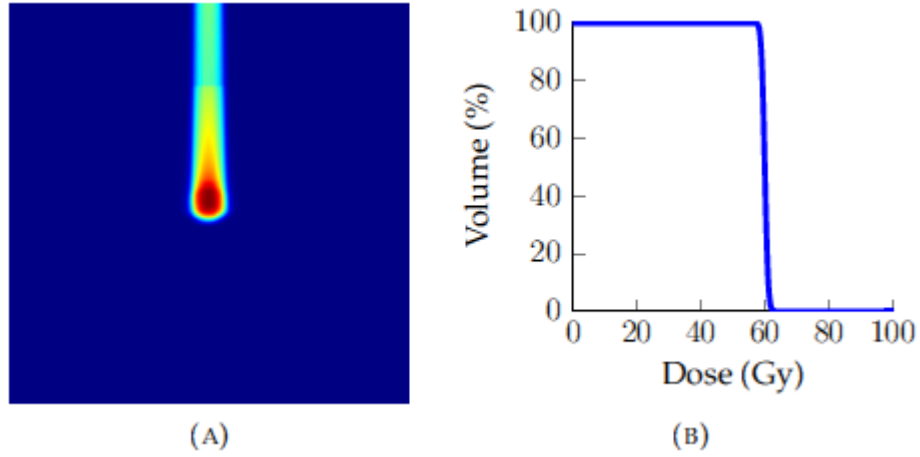


FIGURE 5.1: Results of the reference plan for the rotation test case. (A) Dose map. (B) DVH.

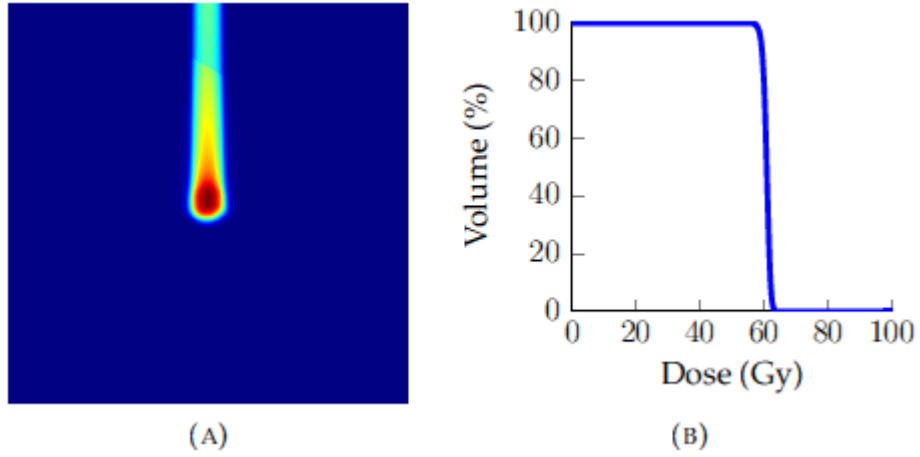


FIGURE 5.2: Results of the adaptive planning for the first test case, rotation of 30° . (A) Dose map. (B) DVH.

is in appendix D. The table 5.3 comprises the statistical features for the reference case (0cm) and the two test cases. We also reported the number of energy layers in each plan, which all use 1425 beamlets.

5.3 Tumor contraction

In this section, we describe the results for the non rigid case obtained by the updated algorithms described in section 4.3.3. With a prescribed dose of 70Gy, results will be judged as satisfactory if D_{95} is above 66.5Gy and D_5 under 73.5Gy.

Rotation	N_{layers}	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
0°	14	58.67	60.06	61.52	2.85
10°	99	58.53	60.19	61.81	3.28
20°	181	58.81	60.52	62.05	3.24
30°	213	58.99	60.92	62.52	3.53
40°	206	58.50	61.64	63.28	4.88
45°	146	57.14	61.25	63.27	6.13

TABLE 5.1: Statistical features obtained for phantom rotation.

Rotation	N_{layers}	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
0°	14	58.67	60.06	61.52	2.85
10°	99	58.40	60.06	61.68	3.27
20°	181	58.36	60.06	61.58	3.22
30°	213	58.16	60.06	61.64	3.48
40°	206	57.00	60.06	61.76	4.75
45°	146	56.03	60.06	62.04	6.01

TABLE 5.2: Results of table 5.1 normalized with respect to the reference D_{50} .

The figure 5.5 represents the dose map and the DVH for the reference case while the figure 5.6 represents them for our best results. The other figures showing the other algorithm's results are in the appendix E. The table 5.5 shows the statistical features of the doses obtained by the different algorithm. As the condition on the D_5 is not satisfied even for the reference case, the normalization was done in respect to the prescribed D_{50} , 70Gy. After this normalization, both condition on D_{95} and D_5 fail to be met. But as the D_{95} is too little by only 0.06Gy, while the D_5 is too big by only 0.18Gy, and as we are not treating any real patient, we decided to overlook this problem.

5.4 Discussion

The results we have at our disposal are feature statistics for several dose distribution. In consequence, they will be analyzed on the features of normalized dose distributions (tables 5.2, 5.4 and 5.6).

The beamlet based approach shows good results for the tumor rigid translation, where it produces a dose distribution on the target volume close to the reference case. The produced plans comprise a

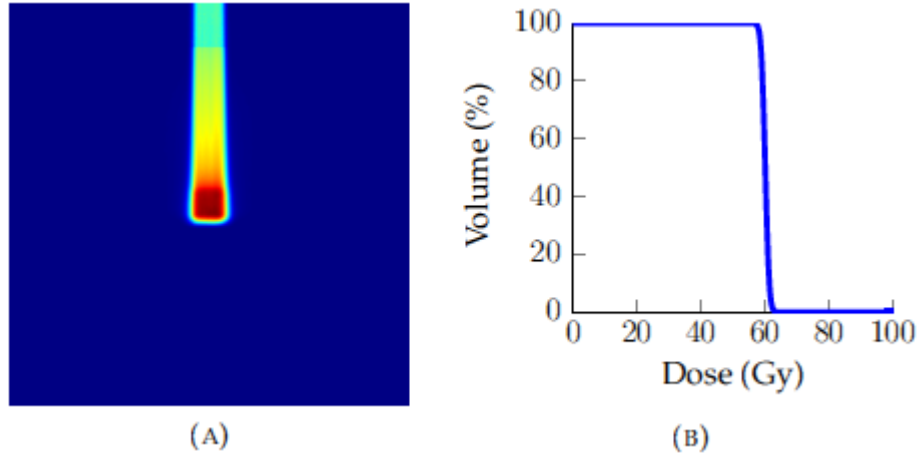


FIGURE 5.3: Results of the reference plan for the translation test case. (A) Dose map. (B) DVH.

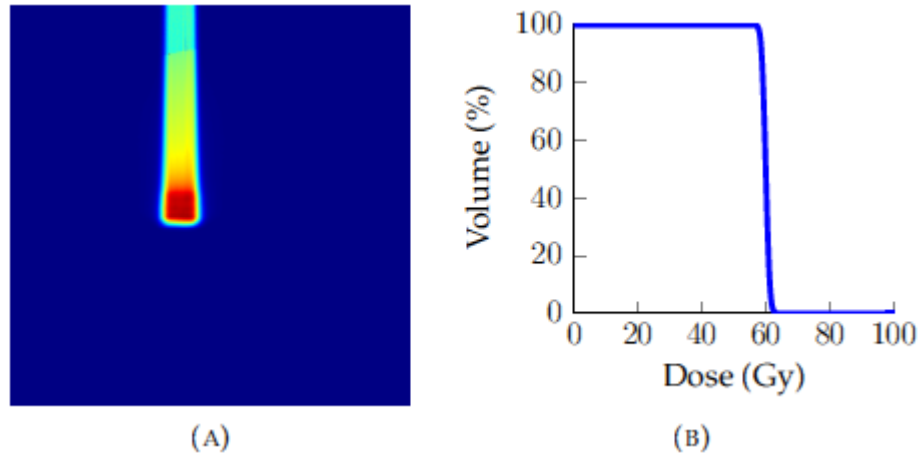


FIGURE 5.4: Results of the adaptive planning for the translation test case, displacement of 4cm. (A) Dose map. (B) DVH.

great number of energy layers (up to 248 with only 14 layers in the original plan), but the number of energy layers seems to be uncorrelated with the performances.

Its results for the case where the whole phantom is rotated are good for limited deformations: the condition on D_{95} and D_5 is satisfied for all rotations except 45° .

But those good results are obtained for very simple phantoms containing only water and simple objects as cubes, sphere and cylinders. There is absolutely no guarantee that this approach would show such performances for real patients, only a hint that this method

Displacement	N_{layers}	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
0cm	14	58.54	60.20	61.87	3.33
4cm	142	58.40	60.05	61.72	3.32
8cm	248	58.11	59.73	61.36	3.25

TABLE 5.3: Results: Statistical features obtained for tumor rigid translation.

Displacement	N_{layers}	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
0cm	14	58.54	60.20	61.87	3.33
4cm	142	58.55	60.20	61.87	3.33
8cm	248	58.57	60.20	61.84	3.28

TABLE 5.4: Results of table 5.3 normalized with respect to the reference D_{50} .

could work for cases where the CTV is not deformed between fractions. Besides, several improvements can be implemented on this method:

- The high number of energy layers may be problematic, as it will increase the treatment delivery time. An additional step regrouping several energy layers close to each other into one may solve this problem.
- Performing a fast optimization using the original weights of each beamlet as a starting point could improve the results.

For the tumor contraction, the best plan is the one with the minimal Gap_{95-5} thus the one built with the first algorithm and no further normalization. Performances are reduced when we normalize the weights, whether we do so of all beamlets at once or when we proceed in smaller groups.

But even with our best plan, the D_{95} is 60.83Gy, 86.9% of the prescribed dose, and the D_5 is 79.37Gy, 113.4% of the prescribed dose. It does not mean that fast adaptive planning is an unsolvable problem in the case of tumor contraction, but only that the sole use of simple linear-like regression methods is not enough to adapt the spots weights.

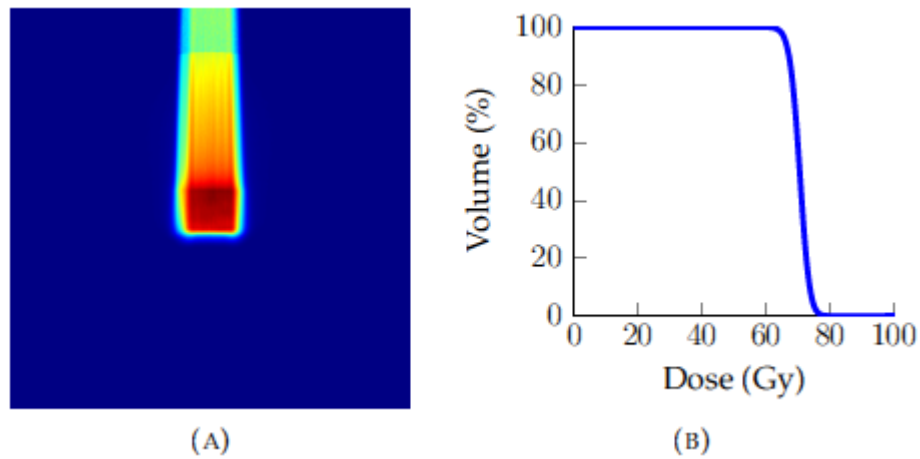


FIGURE 5.5: Results of the reference plan for the tumor contraction reference case. (A) Dose map. (B) DVH.

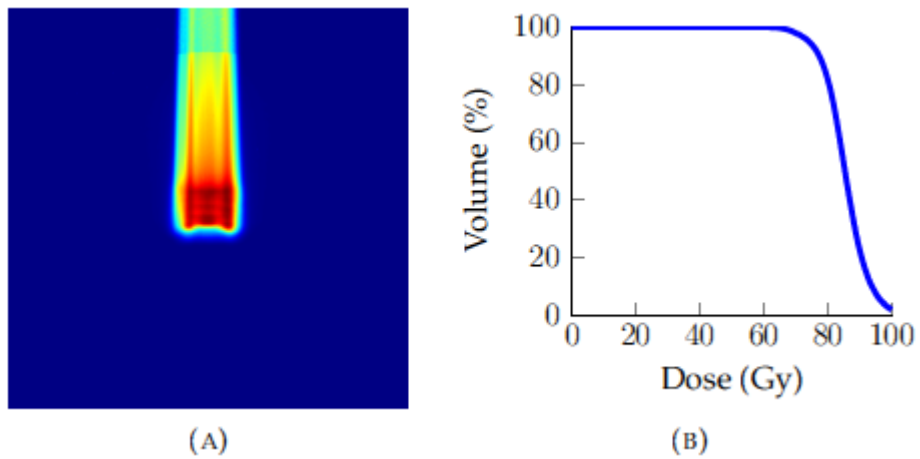


FIGURE 5.6: Results of the first algorithm, without weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH.

This chapter began with a description of the assessment method and features we used to analyze our results. We presented our results before commenting them. The methods we implemented manage to adapt plans if the tumor is not modified, but fail to compute plan delivering a uniform dose to a contracted tumor.

Method	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
Reference case	67.54	71.16	74.90	7.36
One-Raw	74.26	85.45	96.90	22.64
One-Global Normalization	64.59	73.29	86.54	21.95
One-Local Normalization	65.88	76.70	92.14	26.26
Two-Raw	74.76	85.98	102.73	27.97
Two-Global Normalization	54.99	64.52	74.53	19.54
Two-Local Normalization	53.87	64.05	73.89	20.02

TABLE 5.5: Results: Statistical features obtained for non tumor contraction cases.

Method	D_{95} (Gy)	D_{50} (Gy)	D_5 (Gy)	Gap_{95-5} (Gy)
Reference case	66.44	70.00	73.68	7.24
One-Raw	60.83	70.00	79.37	18.55
One-Global Normalization	61.69	70.00	82.65	20.96
One-Local Normalization	60.12	70.00	84.09	23.96
Two-Raw	60.86	70.00	81.41	20.55
Two-Global Normalization	59.65	70.00	80.86	21.20
Two-Local Normalization	58.86	70.00	80.75	21.88

TABLE 5.6: Results of table 5.5 normalized with respect to the prescribed D_{50} .

Chapter 6

Conclusion

In this master thesis, we tried to develop a method allowing a treatment plan modification in order adapt it to physiological modifications while keeping as much information as possible from the original plan. This is the cornerstone of a bigger project whose goal is to perform adaptive planning quickly enough and with performances allowing for bypassing the physician's agreement to continue the treatment. The first step, to compute virtual cases and relevant original treatment plans, was performed thanks to RayStation and MIROpt. The modifications were manually applied to model three different situations: rigid rotation of the phantom for physiological changes in the tissues around the tumor, displacement of the target volume for tumor rigid displacement and creation of smaller target volume for tumor contraction.

In the first two cases, we had to decompose the plan from a structure in layers of energy to a structure in beamlets. This operation required some information from the original plan and others computed through an inverse-raytracing. Then we could displace beamlets so that their position fit the tumor and update the energy required to reach the appropriate depth. The last case required a different approach, as the aim was not to move bragg peaks but to tune their intensity in order to concentrate the dose. With Reggui, we measured the deformation applied on the tumor and used it to compute theoretical new bragg peaks positions. Then we used a linear-like interpolation to update the original, unaltered, beamlets.

Once the plan was adapted, we simulated them by using MC-Square and the results were analyzed computing statistical features recommended by the ICRU.

Firstly we discuss the first algorithm tackling the problem of a

rigid tumor in a non rigid space. For the first case we managed to produce acceptable plans for all rotations except 45° , and the performances tend to decrease with an increasing deformation. In the case of tumor translation, we managed to produce plans as well-performing as the initial ones. These results, though satisfactory in our situation, do not mean that we found the perfect adaption method. Indeed we only used simple phantoms which can not be generalized in any ways. Further tests are needed to verify that our conclusion would still be valid with real clinical cases.

On the other hand, we did we failed to adapt a new plan in the case of tumor reduction. This is not surprising, as we tried to find the answer to a very complex problem with very simple regression methods. This could be solved with other regression method, or by performing additional steps to further modify the plans we compute. For this master thesis we focused on only one strategy of adaptive planning: to preserve as much information as possible from the plan we are trying to adapt, with minimal computation. As cancer therapy often use several treatments together, we could try to combine several methods to achieve our goal. For example, the plans we produce could serve as input for a fast optimizer.

In conclusion, we showed that the use of non-rigid deformation of treatment plan for on-line adaptive protontherapy deserves to be further explored, and also and provided base work to answer it.

Appendix A

Example of a MIROpt output

This appendix contains an example of text file obtained with MIROpt, with all of the information about the computed treatment plan. _____

```
#TREATMENT-PLAN-DESCRIPTION
#PlanName
PlanTest
#NumberOfFractions
35
##NumberOfFields
1
###FieldsID
1
#TotalMeterSetWeightOfAllFields
0.80094

#FIELD-DESCRIPTION
###FieldID
1
###FinalCumulativeMeterSetWeight
0.80094
###GantryAngle
0
###PatientSupportAngle
0
###IsocenterPosition
193.333 277 199
###NumberOfControlPoints
14

#SPOTS-DESCRIPTION
```

```
#####ControlPointIndex
1
#####SpotTunnedID
1
#####CumulativeMetersetWeight
0.44499
#####Energy (MeV)
187.4629
#####NbOfScannedSpots
2
#####X Y Weight
-18.628 -12.9711 0.30472
-18.628 -4.3109 0.14027
#####ControlPointIndex
2
#####SpotTunnedID
1
#####CumulativeMetersetWeight
0.35595
#####Energy (MeV)
185.1464
#####NbOfScannedSpots
2
#####X Y Weight
-21.128 -17.3013 0.16424
-21.128 -8.641 0.19171
```

Appendix B

The importance of simulating a high number of protons with MCSquare

This appendix explores the necessity to simulate a high number of protons with MCSquare in order to obtain a correct DVH. As stated in chapter 3, MCSquare compute the dose with a Monte Carlo method. By using the central limit theorem, one can show that the variance of Monte Carlo decreases proportionally to $\frac{1}{\sqrt{N}}$, with N the number of protons in this case [31]. Thus, simulating a high number of protons increases the probability that the results are significant statistically speaking. The choice of simulating 10^7 protons is thus a compromise between maximizing the significance of the output dose and limiting the computation time.

The figures B.1 to B.3 represent DVHs of doses computed from the same plan, but with respectively 10^2 , 10^5 and 10^6 . The DVH obtained from this plan can be found on figure D.3 along with the corresponding dose.

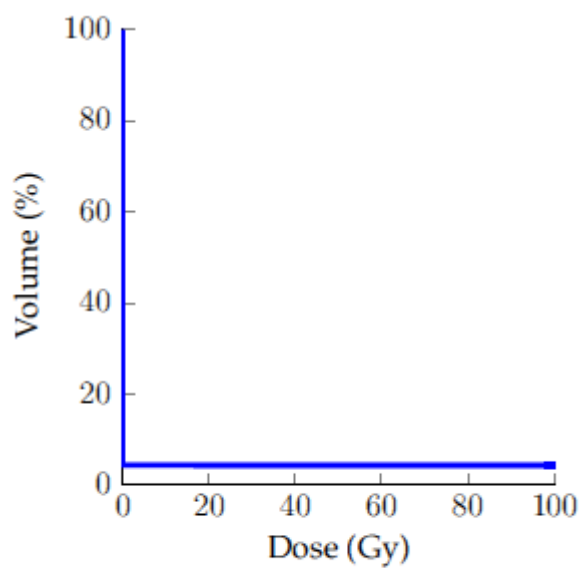


FIGURE B.1: DVH obtained by simulating 100 protons

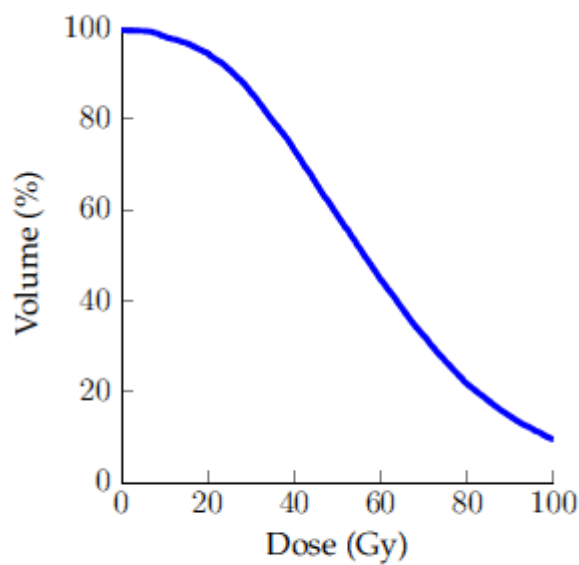


FIGURE B.2: DVH obtained by simulating 10^5 protons

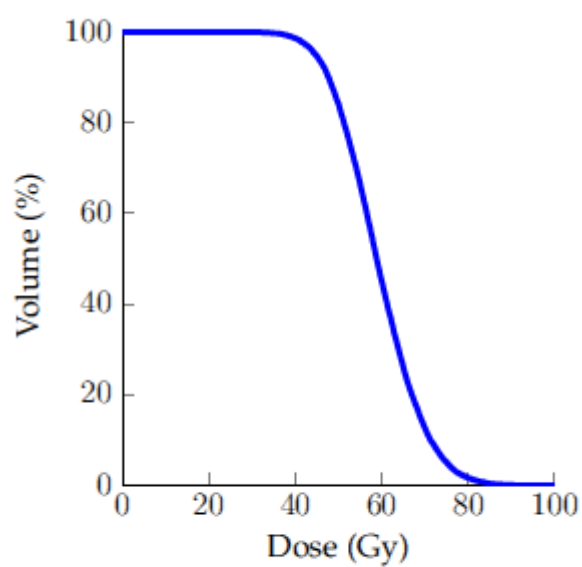


FIGURE B.3: DVH obtained by simulating 10^6 protons

Appendix C

MCSquare outputs for the phantom rotation case

This appendix contains all MCSquares output obtained in the case of the phantom rotation modeling physiological changes around the tumor.

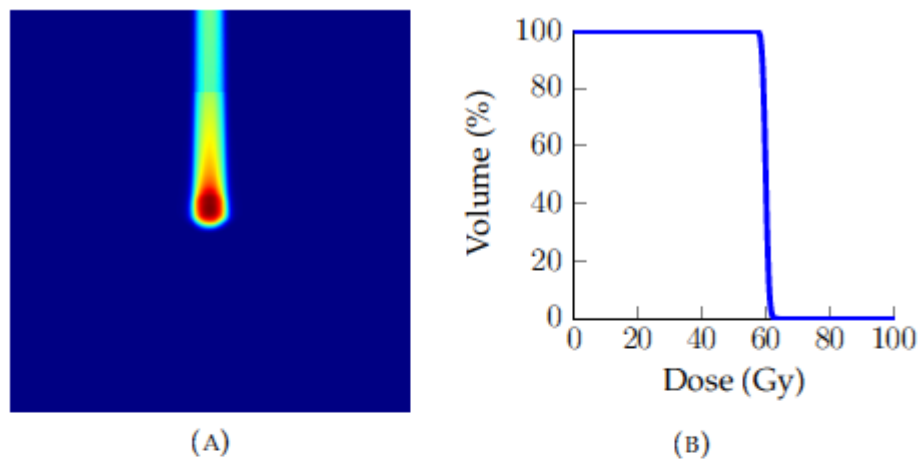


FIGURE C.1: Results of the reference plan for the rotation test case. (A) Dose map. (B) DVH

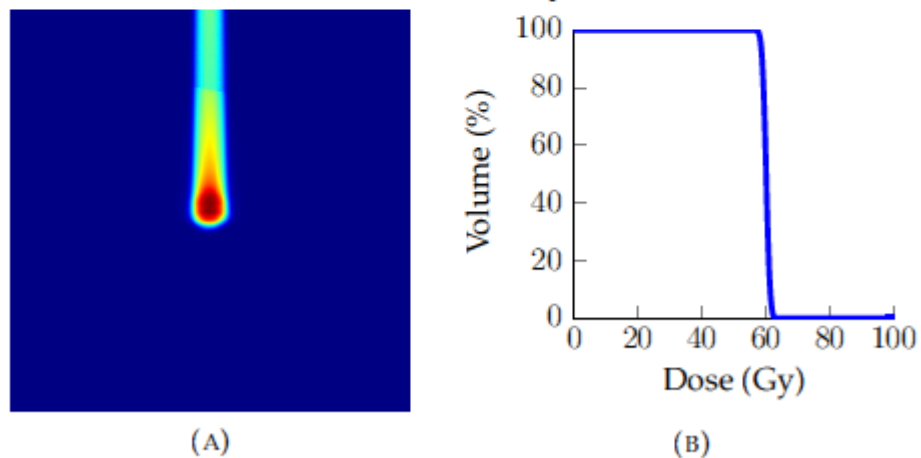


FIGURE C.2: Results of the adaptive planning for the first test case, rotation of 10° . (A) Dose map. (B) DVH

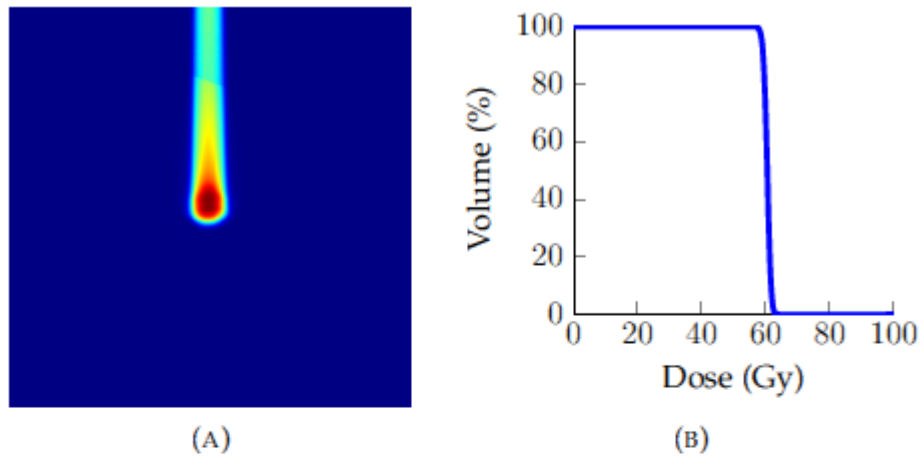


FIGURE C.1: Results of the adaptive planning for the first test case, rotation of 20° . (A) Dose map. (B) DVH

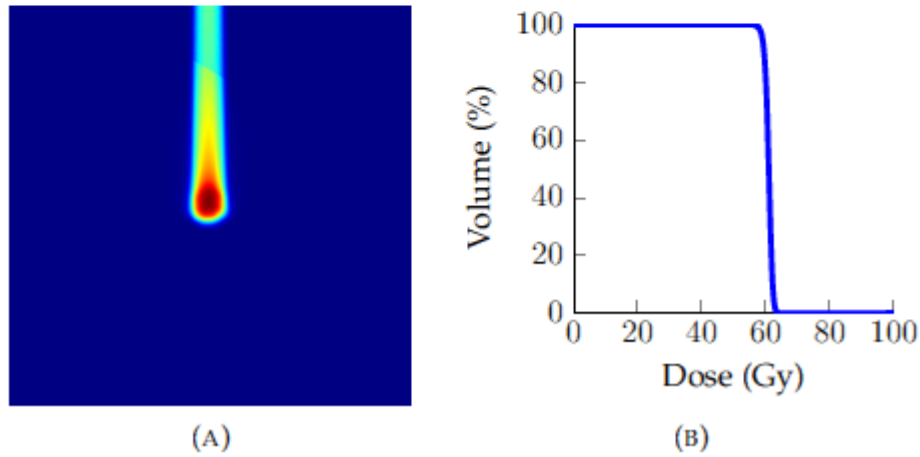


FIGURE C.2: Results of the adaptive planning for the first test case, rotation of 30° . (A) Dose map. (B) DVH

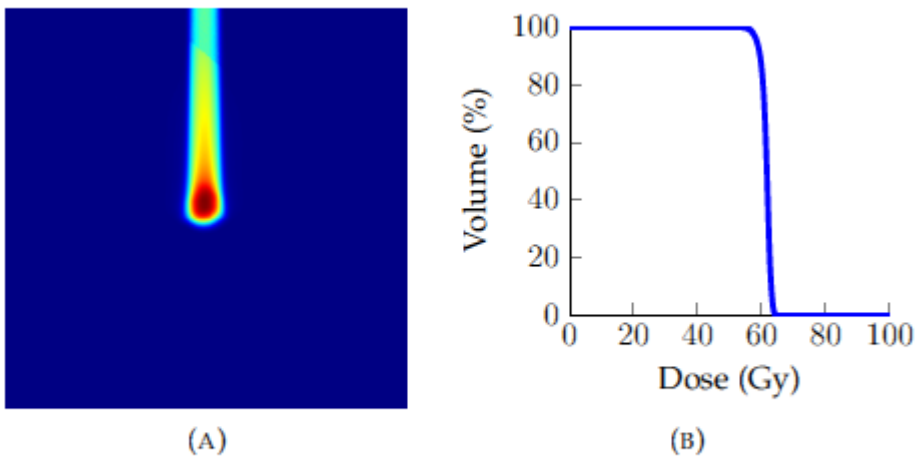


FIGURE C.3: Results of the adaptive planning for the first test case, rotation of 40° . (A) Dose map. (B) DVH

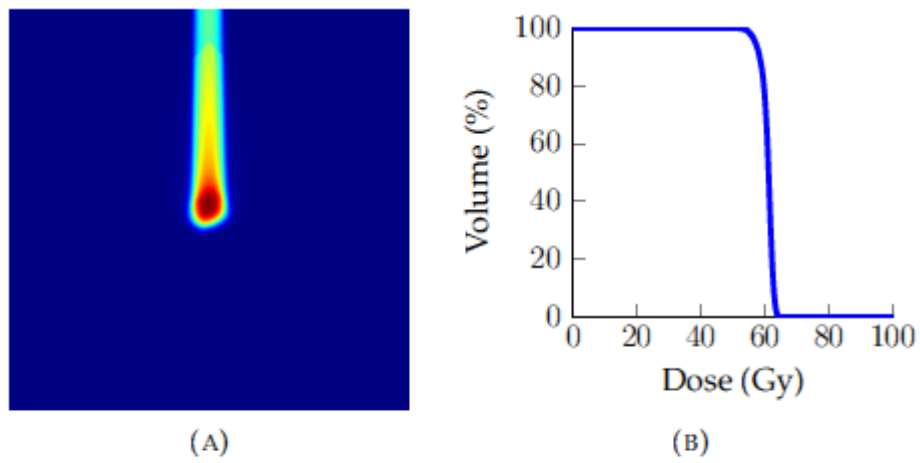


FIGURE C.1: Results of the adaptive planning for the first test case, rotation of 45° . (A) Dose map. (B) DVH

Appendix D

MCSquare outputs for translation case

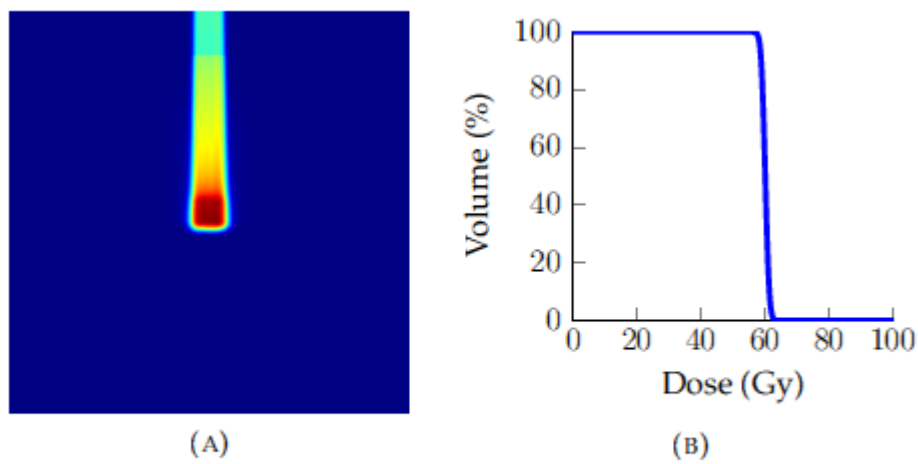


FIGURE D.1: Results of the reference plan for the translation test case. (A) Dose map. (B) DVH

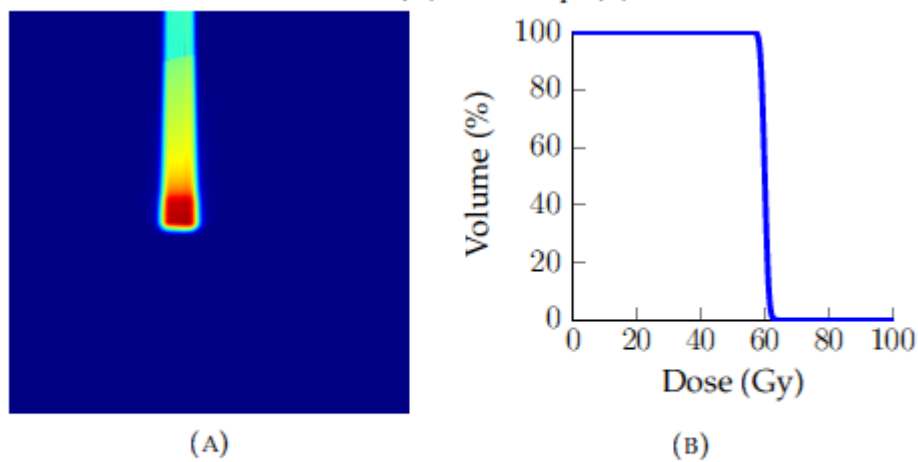


FIGURE D.2: Results of the adaptive planning for the translation test case, displacement of 4cm. (A) Dose map. (B) DVH

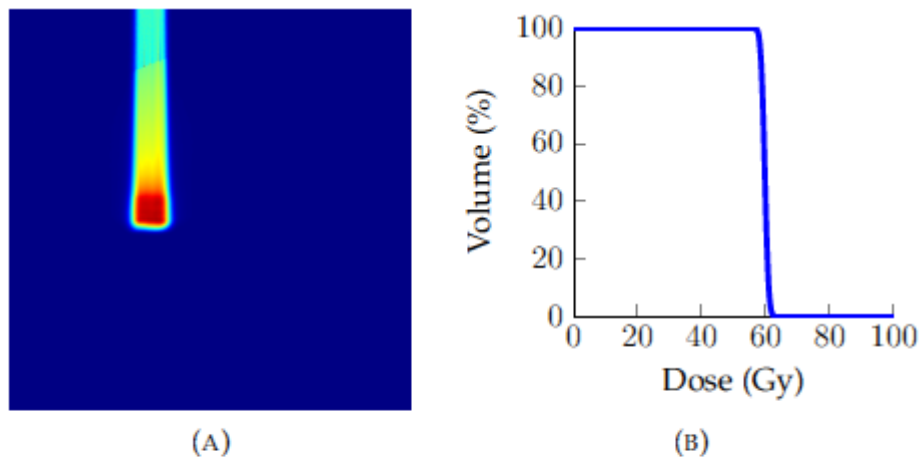


FIGURE D.3: Results of the adaptive planning for the translation test case, displacement of 8cm. (A) Dose map. (B) DVH

Appendix E

MCSquare outputs for tumor contraction case

This appendix contains all MCSquares output obtained in the case of rigid translation of the tumor.

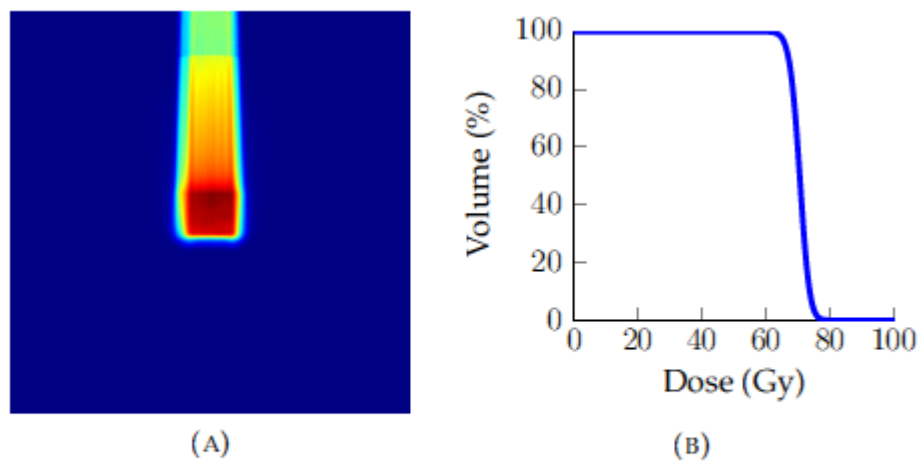


FIGURE E.1: Results of the reference plan for the tumor contraction reference case. (A) Dose map. (B) DVH

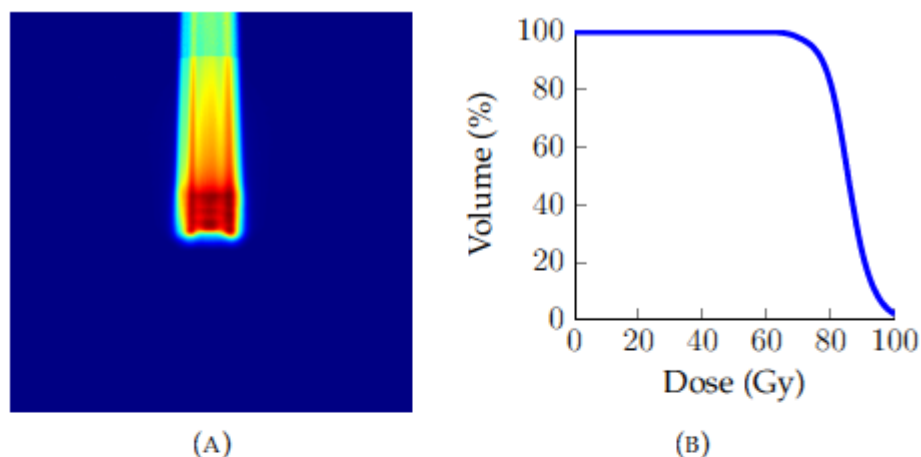


FIGURE E.2: Results of the first algorithm, without weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

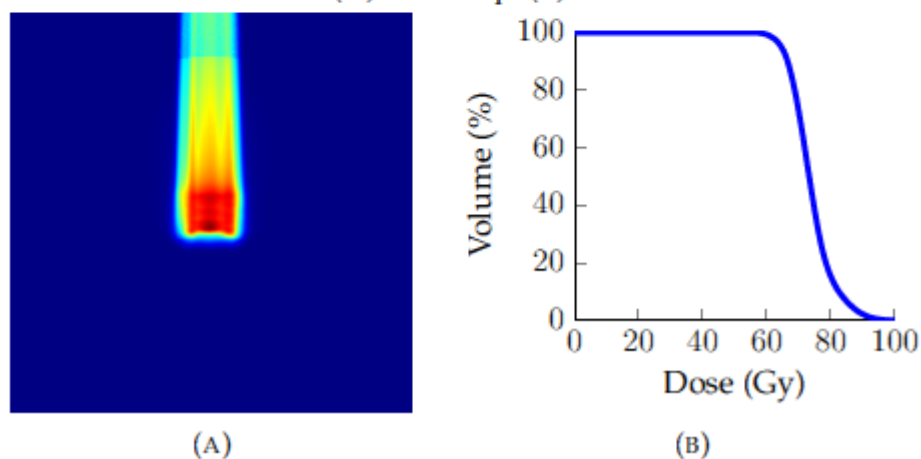


FIGURE E.3: Results of the first algorithm, with global weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

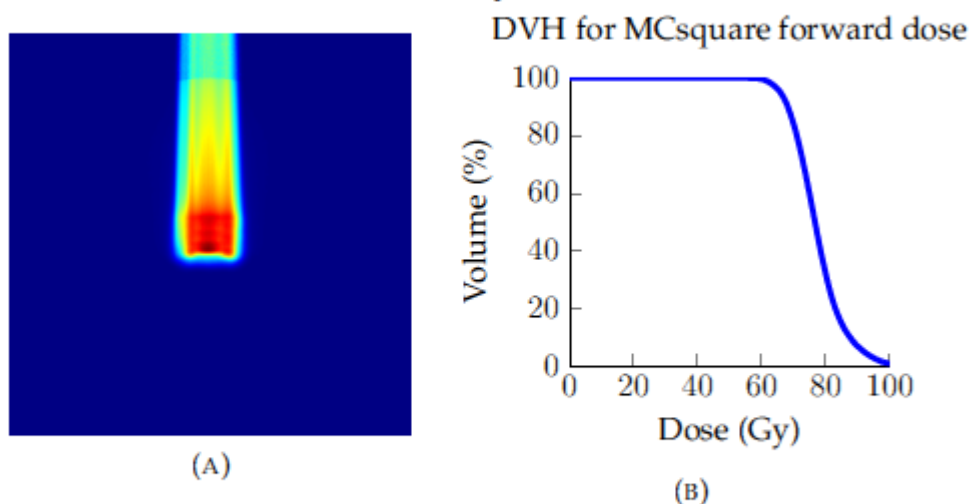


FIGURE E.4: Results of the first algorithm, with local weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

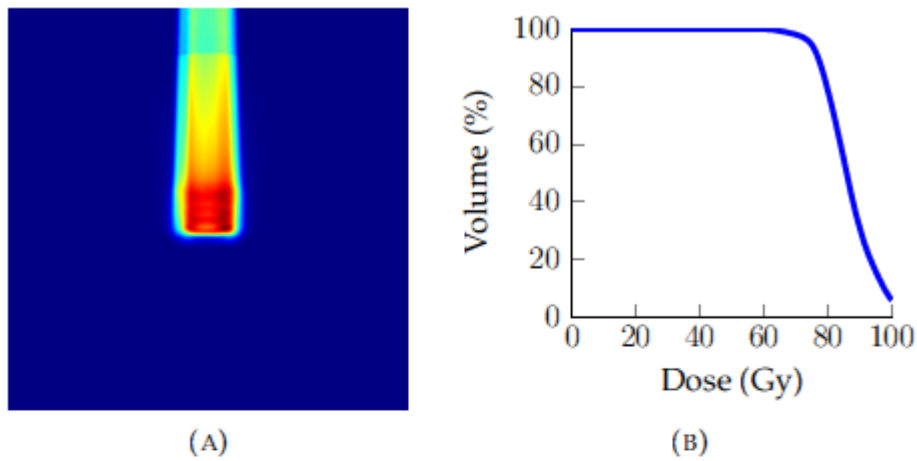


FIGURE E.5: Results of the second algorithm, without weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

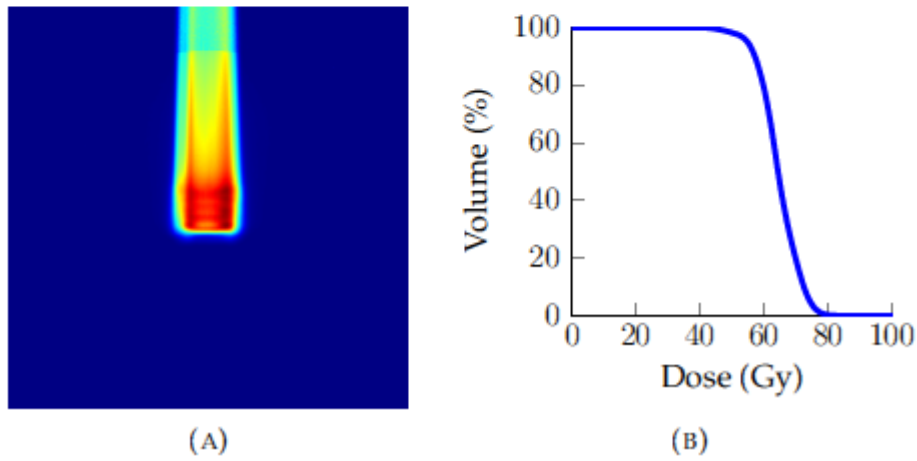


FIGURE E.6: Results of the second algorithm, with global weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

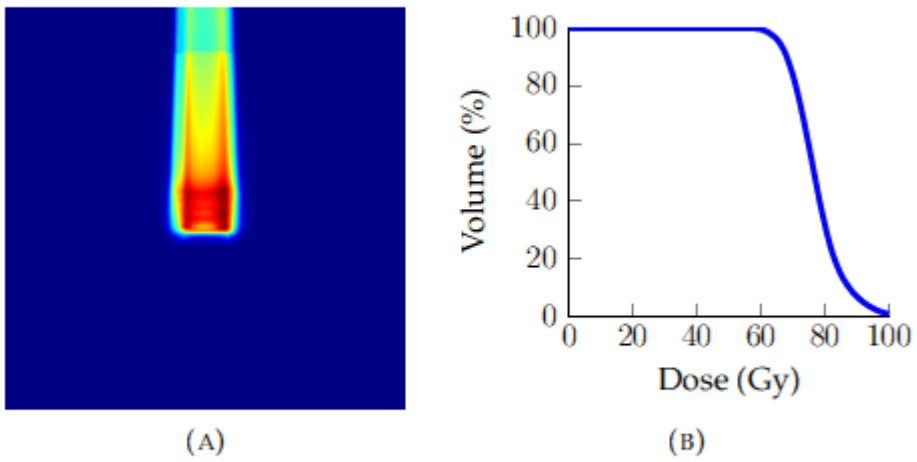


FIGURE E.7: Results of the second algorithm, with local weight normalization, for the tumor contraction test case. (A) Dose map. (B) DVH

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