

Towards real-time image-guided radiotherapy: 3D patient-specific breathing motion models driven by 2D cine-MRI



Damien Dasnoy-Sumell

Institute of Information and Communication
Technologies, Electronics and Applied Mathematics
(ICTEAM)
UCLouvain

A THESIS PRESENTED FOR THE DEGREE OF
Doctor in Engineering Science and Technology

March, 2021

During this thesis, Damien Dasnoy-Sumell was supported by a research grant from the FNRS - Télévie.

PhD committee

Thesis supervisor

Prof. Benoît Macq, PhD, Ir

Institute of Information and Communication Technologies, Electronics
and Applied Mathematics, Université catholique de Louvain
École polytechnique de Louvain, Université catholique de Louvain

President of the jury

Prof. Christophe Craeye, PhD, Ir

Institute of Information and Communication Technologies, Electronics
and Applied Mathematics, Université catholique de Louvain
École polytechnique de Louvain, Université catholique de Louvain

Members

Prof. Christophe De Vleeschouwer, PhD, Ir

Institute of Information and Communication Technologies, Electronics
and Applied Mathematics, Université catholique de Louvain
École polytechnique de Louvain, Université catholique de Louvain

Prof. John A. Lee, PhD, Ir

Molecular Imaging, Radiotherapy and Oncology, Université catholique de Louvain

Institute of Information and Communication Technologies, Electronics and Applied Mathematics, Université catholique de Louvain

École polytechnique de Louvain, Université catholique de Louvain

Dr. Guillaume Janssens, PhD

Ion Beam Applications SA (IBA), Louvain-la-Neuve

Prof. Olivier Debeir, PhD, Ir

Laboratory of Image Synthesis and Analysis, Université Libre de Bruxelles

Ecole Polytechnique de Bruxelles, Université Libre de Bruxelles

Abstract

Treating mobile tumors such as lung or liver tumors with radiation therapy is challenging because the motion induced by respiration has to be considered. Until recently, there was no online and non-invasive imaging solution to follow the tumor motion during a treatment delivery. To ensure the target coverage, security margins are used to extend the irradiated area to encompass the motion, meaning healthy tissues are also hit which can induce undesired secondary effects. In the last few years, a new hybrid device combining Magnetic Resonance Imaging with a radiotherapy treatment unit has been developed. It allows to acquire images and deliver radiotherapy treatment simultaneously. Magnetic Resonance Imaging is the ideal imaging modality for this application because it gives a good soft tissue contrast, the orientation of the images can be chosen, and the image acquisition does not irradiate the patient. In such devices, 2D fast Magnetic Resonance images are well-suited to capture the real-time motion of the tumor. To be used effectively in an adaptive radiotherapy, these MR images have to be combined with 3D X-ray images such as CT, which are necessary to compute the radiation dose deposition. In this thesis, we developed a method combining both image modalities to track the motion on MR images and reproduce the tracked motion on a sequence of 3DCT images in real-time using a motion model. It can be used to drive a treatment delivery in real-time, follow breathing motion and detect irregularities in the breathing pattern.

Acknowledgments

My acknowledgments are first addressed to my thesis supervisor, Prof. Benoît Macq (Université catholique de Louvain, Belgium) who has welcomed me in his wonderful research environment. Thanks to his support and the freedom he gave me to explore my research ideas, these 4 years spent in the imagX-R lab have been really great. I would also like to show my appreciation to my PhD committee Prof. John Lee and Prof. Christophe De Vleeschouwer (UCLouvain) for their guidance and advice and in addition, I would like to thank the entire PhD jury, composed of the PhD committee and three additional members, Prof. Christophe Craeye (UCLouvain), Prof. Olivier Debeir (ULB) and Dr. Guillaume Janssens (IBA).

Working in the imagX-R lab during these past few years has been wonderful. I thank my colleagues Sylvain, Gaëtan, Paul, Antoine, Eliott and Jean with whom it was a pleasure to spend productive days on work or other discussions.

I also thank Rudi Labarbe for his wise advice in the first years of the project, as well as Thierry Metens for his help to choose the MRI sequence we used and Patricia who was a great help to navigate through the administrative part of the work. I should not forget to mention Benoît, PyG, Stéphanie, Simon, Vincent and Anne-So, my colleagues from the lab next door in LLN, who make a good coffee in the secret cafeteria and have helped to make these years a fun experience.

During my PhD I could count on the help of Geneviève Van Ooteghem and Xavier Geets to answer my question and share their knowledge about the medical field, I am grateful for their help. I would like to also thank John Lee and the entire MIRO lab for always finding me a free

desk when I needed to work from Woluwe and for nice midday meals filled with funny discussions.

My gratitude to the Télémie operation and all the people who give a little something to it. It is thanks to these funds that my research was possible.

I will never thank enough my wife Caroline who supports me for so long and my little boy Louis because he is awesome!

And last but not least I would like to express my gratitude to Kevin Souris. He was always there to discuss my research ideas, share his knowledge of the radiation therapy field and give me useful advice. He provided me with IT resources when I needed them and helped me with the implementation for certain part of the software tools I needed. Thank you Kevin!

List of publications

List of the publications which resulted from this thesis

Continuous real time 3D motion reproduction using dynamic MRI and precomputed 4DCT deformation fields

D Dasnoy-Sumell, K Souris, G Van Ooteghem, B Macq

Journal of Applied Clinical Medical Physics 21 (8), 236-248

Locally-tuned deformation fields for 2D cine-MRI-based driving of 3D motion models.

D. Dasnoy-Sumell, A. Aspeel, K. Souris, B. Macq.

Submitted for publication

Proton therapy PBS plan real-time simulation and visualisation tool.

D. Dasnoy-Sumell, K. Souris, G. Van Ooteghem, B. Macq.

ULB-Cancer Research Center annual symposium 2017, Brussels, Belgium

Towards Real-Time proton range verification using dynamic MRI.

D. Dasnoy-Sumell, K. Souris, G. Van Ooteghem, B. Macq.

4D Treatment Planning Workshop annual symposium 2017, Vienna, Austria

4DCT co-synchronized to real-time dynamic MRI.

D. Dasnoy-Sumell, B. Macq.

International Conference on the Use of Computers in Radiation Therapy annual symposium 2019, Montréal, Canada

Continuous 4D motion reproduction using locally tuned deformation fields combination driven by interface tracking on dynamic MRI.

D Dasnoy-Sumell.

Belgian Hospital Physicists Association annual symposium 2020, La Louvière, Belgium

Towards Real-Time PBS dose accumulation observation using dynamic MRI

D. Dasnoy-Sumell, K. Souris, G. Van Ooteghem, B. Macq.

Magnetic Resonance in Radiation Therapy annual symposium 2018, Utrecht, Netherlands

Mechanically-assisted non-invasive ventilation: a step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy.

G Van Ooteghem, D Dasnoy-Sumell, et al.

Radiotherapy and Oncology 133, 132-139

Mechanically-assisted and non-invasive ventilation for radiation therapy: A safe technique to regularize and modulate internal tumour motion.

G Van Ooteghem, D Dasnoy-Sumell, JA Lee, X Geets.

Radiotherapy and Oncology 141, 283-291

Réduction des variations pendant et entre les fractions respiro-induites : le potentiel de la ventilation mécanique orientée vers les stratégies de mitigation du mouvement pour l'irradiation des tumeurs thoraciques ou abdominales

G Van Ooteghem, D Dasnoy-Sumell, X Geets

Cancer/Radiothérapie 23 (6-7), 800-801

Acronyms

4DCT/3DCT	Four/Three Dimensional Computed Tomography
4DCT _c	continuous 4DCT
4DCT _o	original 4DCT
4DCT _p	planning 4DCT
AP	Antero-Posterior
BSSFP	Balanced Steady State Free Precession
CBCT	Cone Beam Computed Tomography
CC	Cranio-Caudal
CT	Computed tomography
CTV	Clinical Target Volume
DVH	Dose Volume Histogram
FID	Free Induction Decay
GUI	Graphical User Interface
GTV	Gross Target Volume
Gy	Gray
ITV	Internal Target Volume
kV	kilo-Voltage
Linacs	Linear accelerators

LR	Left-Right
midP	Mid Position image
MRgRT	Magnetic Resonance guided Radio Therapy
MRI	Magnetic Resonance Imaging
MV	Mega-Voltage
NN	New Navigators
NT	New Trackers
OAR	Organ at Risk
PBS	Pencil beam scanning
PR	Planning Range
PTV	Planning Target Volume
RR	Recomputed Range
SAR	Specific Absorption Rate
SFUD	Single Field Uniform Dose
TE	Echo Time
TPS	Treatment Planning System
TR	Repetition Time
UCLouvain	Université catholique de Louvain
UN	Used Navigators
UT	Used Trackers

Contents

Abstract	7
Acknowledgments	9
List of publications	11
Acronyms	13
1 Context and objectives	19
1.1 Medical Context	19
1.1.1 Cancers and radiation therapy	19
1.1.2 Mobile tumors motion	23
1.1.3 Motion management solutions in clinical practice	25
1.2 Online monitoring	27
1.2.1 External monitoring	28
1.2.2 Internal monitoring	28
1.3 Motion modeling	31
1.3.1 Basic principle	31
1.3.2 3D motion models for MRI guided radiation therapy	32
1.4 Aim and overview of the thesis	32
1.5 Thesis outline	34
2 Magnetic Resonance Imaging and Sequence Selection	37
2.1 Introduction	37
2.2 Magnetic Resonance Imaging General Principles	37
2.3 Our Sequence Choice	44
2.3.1 Gradient Echo Family	44
2.3.2 Balanced Steady State Free Precession	44

2.3.3	Banding Artifacts	46
2.3.4	Specific Absorption Rate Limitations and Technological Progress	47
3	Data management and visualization/analysis tool	49
3.1	Introduction	49
3.2	Data type and acquisition	50
3.2.1	Magnetic Resonance Imaging Data	50
3.2.2	Computed Tomography	53
3.2.3	Deformation fields and mid position image	54
3.2.4	Protontherapy Treatment Plans	54
3.2.5	Contours	55
3.3	Data preparation and linking step	57
3.4	Data visualization and motion tracking GUI	59
3.5	OpenReggui and the Morphons algorithm	71
4	Protons Pencil Beam Scanning plans evaluation using 2D cine-MRI	73
4.1	Introduction	73
4.2	Simulation and visualization tool for real-time proton PBS treatment delivery	74
4.2.1	Context and introduction	74
4.2.2	Materials and method	75
4.2.3	Results and discussions	79
4.2.4	Conclusion and future work	80
4.3	Towards Real-Time proton range verification using dynamic MRI	80
4.3.1	Context and objective	80
4.3.2	Materials and methods	81
4.3.3	Results	83
4.3.4	Conclusion	84
5	Continuous Real-time 3D Motion Reproduction Using Dynamic MRI and Precomputed 4DCT Deformation Fields	85
5.1	Introduction	85
5.2	Method	88
5.2.1	Interface tracking	90

5.2.2	Phase selection method	93
5.2.3	Multi-navigator average phase selection	95
5.2.4	3DCT phase creation	97
5.2.5	Validation	98
5.2.6	Material	99
5.3	Results	102
5.4	Discussion	105
5.4.1	4DCT reliability and inter-fraction	105
5.4.2	MRI-CT spatial registration error effects on the motion model	108
5.4.3	Manual tracker positioning	109
5.4.4	Image acquisition frequency vs resolution and real-time use	112
5.5	Conclusion	113
6	Locally tuned deformation fields for 2D cine-MRI-based driving of 3D motion models	115
6.1	Introduction	115
6.2	Materials and Method	117
6.2.1	Preparation	117
6.2.2	3D image deformation	119
6.2.3	Material	121
6.3	Results	121
6.4	Discussion	126
6.5	Conclusion	126
7	Discussion and Conclusion	127
7.1	Discussion	127
7.1.1	Motion model reliability	127
7.1.2	Manual tracker positionning	128
7.1.3	Real-time uses	129
7.1.4	Other perspectives	131
7.2	Conclusion	132

Chapter 1

Context and objectives

1.1 Medical Context

1.1.1 Cancers and radiation therapy

Cancers are the second cause of death world wide after cardiovascular diseases [1]. It is caused by a mutation in a cell resulting in abnormal cell growth, creating a mass of cancerous tissue which is no longer able to perform its function. Most common cancer sites for women are breast (28.7%), colorectal (12.2%) and lung (9.1%). For men it's prostate (23.2%), lung (14.2%) and colorectal (13.2%) ¹. In total, lung cancer is the one causing the most death with around 20% of all cancer deaths.

Several types of treatments have been developed over the years. The most commonly used are surgery, chemotherapy and radiation therapy, with sometimes a combination of several methods [98]. Radiation therapy and in particular external beam radiation therapy is useful in about 50 percent of patients [101] and is the treatment method at the base of this work.

Radiation therapy consists in hitting the tumor with high energy rays to destroy the DNA of tumor cells and stop them from proliferating. As tumors are surrounded by healthy tissues, an accurate targeting is important. It is not possible to entirely avoid hitting healthy cells but the challenge is to give enough radiation dose to the target while keeping

¹<https://ecis.jrc.ec.europa.eu/>

the dose given to healthy tissues to a minimum [5]. The most common version of radiation therapy is simply called radiotherapy. It relies on linear accelerators (Linacs) to create high energy photon beams. Several beam orientations can be used to better distribute the dose to healthy tissues and to have more angle options for a better target coverage.

After being irradiated, healthy tissue cells recover better than tumor cells. To maximize this effect, a complete treatment is usually split into several fractions delivered on different days. For a single fraction, the patient stays between 20 to 30 minutes in the treatment room but the actual irradiation takes only around 3 to 5 minutes depending on the tumor size and the number of beam angles used. The rest of the time is spent to prepare and setup the patient as precisely as possible in a reproducible treatment position.

Proton therapy is a particular sort of radiation therapy that uses protons instead of photons. Protons interact differently than photons with tissues, which results in a different dose deposition profile [Figure 1.1]. They deposit a maximum of dose at a particular point called the Bragg peak, after which they stop and no dose is delivered afterwards. The depth at which they stop is called the proton range. It depends on their initial energy and the composition of the tissue they pass through. This presents an advantage as the goal is to deliver a high dose to the target and a dose as low as possible around it. The most advanced proton therapy method is the Pencil Beam Scanning (PBS). The principle is to separate the treatment into a succession of very fine beams called spots, which can be administered one at a time to a specific position and energy to cover the entire target. Protons can potentially have a better accuracy than photons and by such being more adapted to target small tumors or tumors close to organs at risk. But it is a double edge sword, protons are more sensitive to small motion and tissue density changes and each error will have more impact on the outcome.

As a radiation therapy treatment is not something that can be driven in real-time easily, a treatment must be carefully planned in advance. The role of the Treatment Planning System (TPS) is to find the best combination of beam direction, shape and duration to cover the target with the prescribed dose as homogeneously as possible while sparing Organ At Risks (OAR's). To do so, the TPS receives a planning image

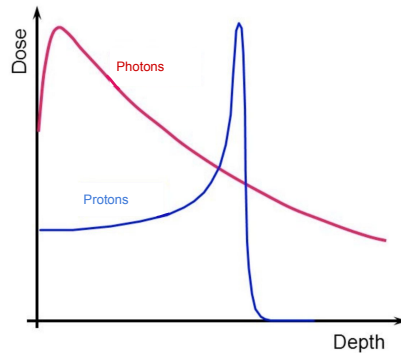


Figure 1.1: Representation of the dose deposition profile for a photon and a proton interacting with matter in function of depth in the tissue. The photon delivers more dose initially, then the delivered dose decreases in an approximately linear way until it passes through the patient completely. The proton dose is lower at first, then rise abruptly to reach the Bragg peak where the proton stops.

that was acquired previously on the patient in the same position and conditions as the treatment. On this image, the target contour as well as OAR's contours are delineated. It is a tedious job done by hand by doctors on a contouring software. It takes a lot of time to do this manually and more and more research is aiming at automating this process [59, 42, 99].

Then, different target volumes are defined as successive expansion around the target to account for different uncertainties [Figure 1.2]:

- The Gross Target Volume (GTV) is the tumor visible on images. It is the one manually delineated by a physician.
- The Clinical Target Volume (CTV) is an extended GTV (a few mm) which account for suspected tumor cells spreading but invisible on the images.
- If the target is located in an area subject to motion such as lungs, the internal margins (sometimes called motion margins) can extend the CTV to encompass the motion amplitude. There are different methods to define them. The Internal Target Volume

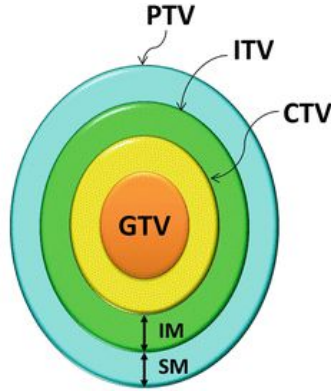


Figure 1.2: Schematic representation of the different target volumes extension from the original Gross Target Volume (GTV), manually delineated by a medical doctor. The Clinical Target Volume (CTV) accounts for invisible tumor spreadings, then the Internal Target Volume (ITV) to account for motion using the Internal Margins (IM), and finally the Planning Target Volume (PTV) to account for uncertainties in the setup with the Setup Margin (SM).

(ITV) is the union of the different CTV's for every image in a 4D (3D time series) image acquired before the treatment. The midP image can also be used for photons (see chapter 3) to define an average position CTV and then extend it based on the deformation fields computed in the midP image creation method [103]. And for protons, robust optimization can be used to extend the CTV base on a series of uncertainty scenarios (cf. section 1.1.3).

- Finally, the Planning Target Volume (PTV) extends the previous volumes with margins to account for setup errors which are the errors caused by small differences in the positioning of the patient on the treatment table [103].

With the target volume, the TPS also receives the objective dose and constraints on the OAR's. For example the stomach cannot receive more than 18 Gy (The Gray (Gy) is a unit of ionizing radiation) in average over 10 cc of volume and a maximum of 32 Gy of dose locally. Once each constraint has been encoded, the TPS starts the optimization

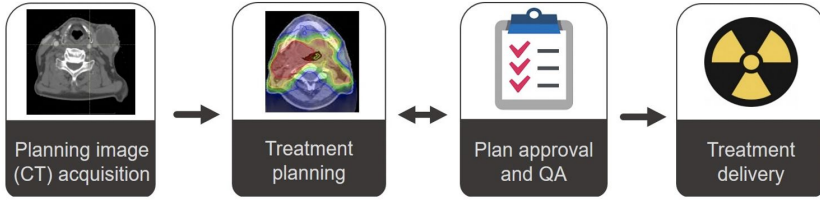


Figure 1.3: Schematic representation of the radiation therapy treatment workflow. First the planning image acquisition, then the treatment planning where the contouring and optimisation are done, followed by validation and finally delivery.

process to try to find a way to cover the target and avoid the OAR's as best as possible. When a solution is found, it must be validated by a radiotherapist and if approved, the treatment can be scheduled [Figure 1.3].

In standard radiotherapy with photons, the PTV is the one given to the TPS. For protons, it is now usually the CTV combined with robust optimization (cf. section 1.1.3).

Using these extensions of the original GTV, the target coverage is assured but healthy tissues are also hit. For target close to the diaphragm where the motion is usually maximum, the PTV volume can be several times the size of the CTV [Figure 1.4].

While the CTV extension is biologically related, the motion margins and PTV margins are necessary because we still lack the technology in software and hardware to position the patient better and to track and treat the target in real time with precision. Therefore, uncertainties must for now be compensated by large security margins.

1.1.2 Mobile tumors motion

While trying to target abdominal or thorax tumors such as lung or liver tumors, the tumor motion induced by the breathing action and displacement of the diaphragm must be taken into account. Two different motion timings must be considered:

- **Inter-fraction motion** is the motion happening in a slower time

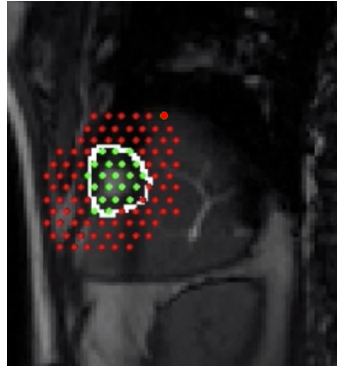


Figure 1.4: Example of size difference between the PTV and the CTV for a proton PBS treatment plan. The PTV is the area covered by the red spots and the CTV which is the real tumor is only the area contoured in white and covered by the green spots.

scale, over a period of days or weeks. This can be due to anatomical changes in the tissues around the tumor due to the dose received, the tumor itself growing or shrinking, the patient weight loss, or simply a slight displacement of the organs due to the different movements of the patient.

- **Intra-fraction motion** is the motion happening during a treatment fraction. These movements are of the order of magnitude of a tenth of a second to a few minutes, such as the motion induced by the respiration or coughing.

From these two types, the intra-fraction motion is the main concern for the work presented in this thesis. It can be split again in two categories:

1. **Periodic or semi-periodic motion:** The respiratory cycle is the main cause of periodic or semi-periodic motion. The region around the diaphragm is usually the region that shows the greatest range of motion but the impact goes from the top of the lung to the bottom of the abdomen. On a smaller scale and higher frequency, the cardiac cycle also adds to these periodic movements [91]. Different studies using different methods of measurements

have shown that a lung tumor can move up to 5 cm in the Cranio-Caudal (CC) direction, as well as around 2 cm in the Anterior-Posterior (AP) direction and 1 cm in the Left-Right direction (LR) [47]. But their motion is not easy to predict nor correlated with the motion of something else in a consistent way [97]. For liver, which is right under the diaphragm, it can also get to 5 cm in the CC direction, around 2 cm in the AP direction, and is usually smaller than 1 cm in the LR direction [28, 47, 81]. Again, the variability between patients is important and it is not really possible to derive useful guidelines to predict the motion [18]. The amplitude and frequency can vary between patients and also for the same patient intra-fraction. Irregular pattern with apneas and coughs can also occur.

2. **Baseline shift/drift:** A baseline shift or drift is a systematic shift in the position of an organ or tumor, meaning the average position over the cycles of the periodic motion is shifted [100, 56, 108, 37]. That usually occurs between fractions but it can also appear on a time scale of the order of a few minutes. It can be caused by gastrointestinal activity such as peristalsis or bladder filling.

The two types can also happen simultaneously, as represented in figure 1.5.

1.1.3 Motion management solutions in clinical practice

Different approaches have been developed and can be used to tackle the motion related issues online (during a fraction delivery) or offline (before the treatment or in between fractions). Here we will use the term *online* to describe a method that can be use while the beam is active, and not in the conventional way which is usually *in the treatment room*.

- **Breathing regulation (online):** The idea is to regularize the breathing amplitude of a patient. It can be done by training the patient to breathe in a synchronized manner with a sound that he hears through an audio headset [33]. Another option is a non-invasive ventilation technique using a mask to force a certain breathing pattern [73].

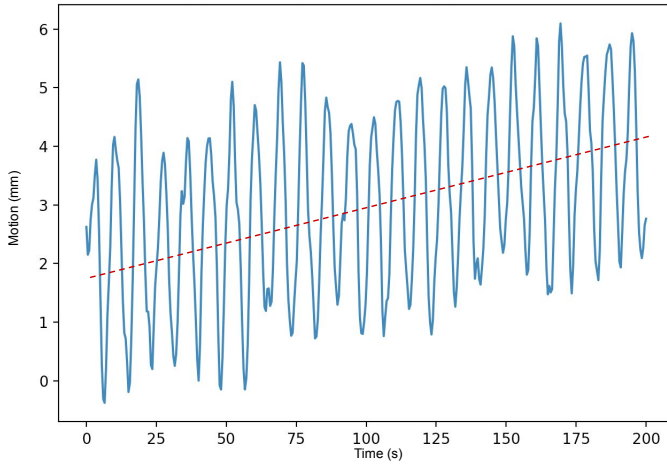


Figure 1.5: Representation of a periodic motion signal over time with an additional baseline shift shown by the dashed line.

- **Motion reduction (online):** The principle is to limit the motion amplitude. It can be achieved using an abdominal compression belt [28, 57] or also with a non-invasive ventilation technique using a mask, this time to force a breathing pattern with small amplitude [72], or by using successive breath-hold of around 30 seconds during which the beam can be turned on [69, 11].
- **Gating (online):** Gating is one of the few real-time application used today during a treatment fraction. The principle is to wait for a specific moment in the periodic movement of the target during which the position of the target is known with a high degree of confidence. During this particular moment in the periodic motion, the beam can be activated [47]. It relies on a surrogate signal acquired in real-time, and correlated with the target motion. The downside is that it can increase the treatment duration, especially if the target is not in the area of interest often enough.
- **Tracking (online):** Tracking is the most advanced online method, but also the most challenging. It consists in tracking the tumor location or a surrogate that gives a good enough approximate tumor location in real-time, and use this information to follow the

tumor with the treatment beam. It is potentially the way to go to completely remove the motion margins, which could drastically reduce the dose given to healthy tissues. It has been developed in research in different ways [108, 87, 82, 15, 93, 78, 25] using different hardware solutions (cf. section 1.2), but is in its current state usually using invasive implanted markers and not reliable enough to remove motion margins in clinical routine practice. Moving towards efficient tracking solutions is the motivation behind the methods proposed in this thesis.

- **Adaptive radiotherapy (offline):** The acquisition of new images in between fraction can sometimes show that the treatment initially planned is no longer adequate, for example if inter-fraction motion happened. The principle is then to start over the treatment planning process based on the new images, with the objective dose to the target adapted in function of what was already delivered.
- **Robust planning (offline):** Robust planning consist in making a treatment plan more robust to uncertainties. The TPS receives, on top of the usual information, a certain number of uncertainty scenarios such as small shifts and rotation of the patient position or irregular breathing states. Then, the optimization of the treatment plan must also covers the requirements in the event that one of these scenarios occurs.
- **Repainting (offline):** Repainting is specific to proton therapy PBS treatments. The methods consists in changing the treatment plan such as the spot pattern is repeated more than once, but with a lower dose [107]. It can be used to reduce an issue that can appear with PBS treatments called the *interplay*, where the delivery of the spot pattern and the target motion interfere, creating areas of overdosage or underdosage [34, 8].

1.2 Online monitoring

This section gives an overview of current monitoring methods available to observe or measure movements during treatment. It will be listed in two groups, internal monitoring which gives signals from the interior of a

patient's body, or external monitoring which gives an information about the patient surface motion. A combination of internal and external monitoring is also possible.

1.2.1 External monitoring

External signal acquisition presents the advantages of non-invasiveness and high acquisition frequency. The downside is that it only gives precise information about an external part of the patient anatomy. They serve as surrogate signal that relies on a supposed internal/external correlation between the given signal and the target inside the patient [10]. Depending on the site it can be really reliable, for example brain tumors whose movement is very strongly correlated with the movement of the skull, but for abdominal and thoracic area the internal motion is not as well correlated to external surrogates. [6].

- **Infrared reflectors:** This method uses infrared camera and infrared reflector to follow the position of the reflectors placed on a patient skin. It can be used for gating [104].
- **Optical surface monitoring:** A laser grid is projected on the patient surface and monitored using cameras. The deformation of the grid is used to re-create the entire surface, that can then be compared with a planning image ².
- **Spyrometry:** The principle is to make the patient breathes through a mouthpiece that allows to measure the air flow going in and out. The lung volumes can then be evaluated and used to predict the anatomy using a motion model [65].
- **Pressure belt:** A belt is place around the patient abdomen in which a pressure sensor measures the belt tension. The variation in tension gives information on the current breathing state that can be used to drive a gating method.

1.2.2 Internal monitoring

Internal online acquisitions is the key to *see what we treat as we treat it* [10]. The recent developments in MRI guided radiotherapy (MRgRT)

²<https://www.visionrt.com/products/alignrt/>

and in particular online MRI is what motivated our research but other methods also exists and keep improving as well.

- **kV or MV x-ray imaging:** This modality is the most widespread. The majority of treatment rooms are equipped with at least one basic system allowing simple x-ray projections, because it is used also for patient alignment previous to treatment. More advanced options also exist, such as stereoscopic options with multiple perpendicular planes, as well as Cone Beam Computed Tomography (CBCT).

One disadvantage is that the soft tissue contrast of x-ray images is bad and most tumors are not easily visible. To work around this problem, metal implants called fiducials are often implanted in or around the target. They give a high contrast in images and can be tracked very easily. The implants are tracked instead of the tumor and the tumor position is derived from the implants positions [60, 31, 9]. The downside is that placing the fiducials is an invasive procedure. Also, x-ray imaging irradiates the patient as well, the dose due to imaging should then be limited in case of continuous use.

The Cyberknife³ is a particular implementation with kV x-ray projections acquired every 10 seconds combined with a surface monitoring. A motion model is used to derive the tumor position from the surface monitoring and the x-ray images are used to check every 10 seconds if the correlation between tumor position and surface monitoring is still valid. The beam angle and position can be moved to follow the predicted tumor position in real-time.

- **Ultrasound:** Ultrasound imaging can also be used to monitor organs motion during treatment. It gives a good soft-tissue contrast, resolution and frequency of acquisition [53, 36]. The downside is that it is difficult to place the ultrasound probe reproducibly. It should be placed in contact with the skin with almost constant pressure so as not to cause displacement itself.
- **Electromagnetic transmitters:** These transmitters are active implants that can be activated to emit a signal from inside the

³<https://cyberknife.com/>



Figure 1.6: Elekta Unity MR-Linac. Elekta ©

patient [3]. Using multiple transmitters with different frequencies, the target position can be deduced throughout the treatment.

- **MRI:** In the last decade, hybrid hardware solutions combining MRI and photons radiation therapy have been developed [79]. Two different systems are commercially available: ViewRay was the first one to commercialize their system with the MRIdian⁴ [67], then Elekta followed with their Unity⁵ system [55] [Figure 1.6]. Several other options are in development [58, 29].

MRI offers a good soft tissue contrast, does not use fiducials and no imaging dose is given to the patient. The MRI scanner of an MR-Linac can be used to acquire 3D images as standard MRI scanners, but not during treatment. The acquisition speed limits for now the intra-fraction possibility to a small set of 2D slices acquired repeatedly (called dynamic MRI or cine MRI). The slices can be chosen in any position or orientation. The downside is that it cannot be used in the case of metallic prosthesis or electronic devices like pacemakers. Note that the MRI scanners that are combined with Linacs are a little behind in terms of performance and

⁴<https://viewray.com/discover-mridian/>

⁵<https://www.elekta.com/radiotherapy/treatment-delivery-systems/unity/>

features compared to state of the art MRI scanners only dedicated to imaging.

For protons, hybrid MRI-protons treatment delivery systems are not available yet. Combining the two technologies is really challenging. Protons delivery on its own uses magnets which can alter the homogeneity of the magnetic field in the MRI scanner, and the protons being charged, they are deflected by the Lorentz force in a magnetic field. Nevertheless, some early hybrid machines design, as well as studies on proton beam deflection in magnetic field have been made [70, 66, 41]. Due to their particular dose deposition profile and nature, combined with the PBS method, protons could benefit even more than photons of such an hybrid device. This is the reason why we decided to use proton plans for our experiments, and see if we could find out what could be the potential uses of online MRI for protontherapy.

As this was our choice of modality and motivation for our research project, more information about MRI is given in chapter 2.

1.3 Motion modeling

1.3.1 Basic principle

In a system where the set of situations resulting from possible motion is P , a motion model is a method m which can, from a set of initial states X , and a set of observations O create a new state $\hat{X}_i = m(X, O) \in P$.

It can be used for prediction application to predict a future state in time based on previous observations, in this case, $\hat{X}_{t+1} = m(X_t, O) \in P$ where O contains information about the past.

Or it can be used to create new states $\hat{X}_i = m(X, O_i) \in P$ by interpolating or extrapolating the set X . In this case O_i is a specific observation linked to X_i . It is this second option that we will use, predicting the future state is not our objective.

1.3.2 3D motion models for MRI guided radiation therapy

In particular for radiation therapy, the motion models that we are interested in use as initial states a set of images acquired previous to the treatment. The image set contains a number of samples distributed over one or a few periods of the respiratory cycle, which is the main cause of intra-fraction movement. A *patient-specific* motion model will only use images from the treated patient, while an *atlas-based* motion model will use a database of multiple patients or volunteers to build an average motion. Due to the variability in patient anatomies and breathing-induced motion, on top of the fact that images are acquired anyway for the treatment planning step, the trend for radiation therapy has been towards patient-specific motion models.

A set of 2D or 3D images where the position of the target is known form the initial states X of the motion model. In addition to that, we need a driving signal to get the observation O_i necessary to built the predicted state $\hat{X}_i = m(X, O_i) \in P$. The driving signal can be of different nature, it can come from external monitoring like surface tracking, or internal monitoring like electromagnetic transmitters or intra-fraction imaging (cf. section 1.2).

In our case, the motion model will use a set of 3D Computed Tomography (3DCT) images as initial states, and the driving signal will be 2D images acquired online with an MRI scanner. Even though MRI technology is steadily advancing, it is not yet possible to obtain 3D images at high enough frequency to follow the respiratory movement, so the driving signal will come from high frequency 2D slices.

1.4 Aim and overview of the thesis

Real-time MRI-guided radiation therapy would certainly help the field improving the quality of the treatments. A better soft tissue real-time observation should help designing new real-time guided treatment methods with lower or no motion margins, as well as lower setup error margins. This would result in sparing more healthy tissue and reduce overall toxicity and side effects of treatments. MR-Linacs are still very young

and not very common. In result, not so much patient data or potential uses of these new devices have been investigated, there is a whole new world to explore. 2D driving of 3D motion models seems particularly interesting using 2D MRI slices because they presents multiple advantages in image quality and imaging irradiation, as well as the slice orientation choice they provide which can be easily modified in function of the target motion or treatment beam angles.

In this thesis, we aim at using 2D dynamic MRI image series to track in real-time the abdominal or thoracic movements that occur in patients when they lie on a radiation therapy treatment table. It will then be possible to evaluate the effect of these movements on the delivered dose. A complete 3D MRI image cannot be acquired with sufficient frequency at the moment but using only 2D frames, it is possible to get to the desired acquisition rate. We created a method that uses 2D MRI images to drive a 3D patient-specific motion model to get the 3D motion. From the different MRI imaging options, we decided to use the *Balanced Steady State Free Precession* (BSSFP) MRI sequence. This sequence can be used with sufficient acquisition frequency, spatial resolution and contrast to see and follow the tumor and/or organs visible in the images. Since the start of our work in 2016, other groups have proposed similar methods using also BSSFP sequences to be used as retrospective dose accumulation tools or target tracking [79, 32, 95], but not fast enough to be used online or suitable to compute the delivered dose. Therefore, we decided to put a particular emphasis on real-time use and speed. We developed a semi-automatic method with an initial manual intervention that allowed us to design a simple and nearly instantaneous way to extract the useful information from the 2D MRI slices, and use them in the motion model. The motion model is used to deform a 3D reference image using pre-computed deformation fields to continuously reproduce the patient anatomy in 3D [Figure 1.7]. The 3D image that is deformed is a CT image on which the deposited dose can be computed. Then, we developed a method to add on top of this first approximation to improve the precision of the 3D reproduced motion. This additional step combines multiple deformation fields to adjust locally the matching 2D MRI - 3DCT and improve the results precision. To reach these goals, we had to develop ourselves a software tool to visualize in real-time treatment

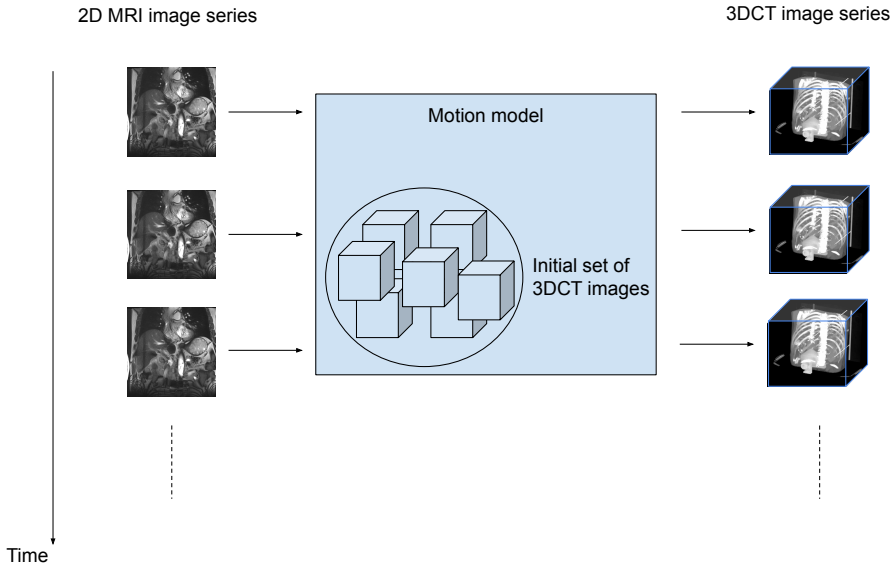


Figure 1.7: Representation of the real-time application. Each time a new MRI image is available, it is given to the motion model in which the initial set of 3D images are used to create a new 3D image that match the motion observed on the 2D MRI.

deliveries and measure motion amplitude on time image series using a simple but robust to noise interface tracking method.

1.5 Thesis outline

This dissertation is conceived as a collection of chapters from published and submitted articles. Therefore, a few points may be introduced redundantly in the different chapters.

We started in this chapter by introducing the medical context. The radiation therapy basic principles, as well as what is currently available to monitor breathing motion online and the basics of motion models. The goal of this thesis is to investigate how to use 2D cine-MRI in real-time to guide radiation therapy treatments. Chapter 2 will give more information about the MRI technology and in particular why we chose

the BSSFP sequence and its basic principles.

As collecting and managing data was a time consuming part and complicated part of this work, we explain in chapter 3 the different data types and processing methods that were necessary for our research, as well as the software tools that we developed ourselves to achieve our goals.

Chapter 4 presents a method to use MRI frames to compute real time statistics to evaluate the quality of a PBS proton treatment, and a method to recompute the range of protons passing through the MRI image while considering the breathing motion.

At this stage of the thesis, discussions with doctors led us towards the idea that 3D motion reproduction was necessary. The method in chapter 4 does not allow the direct computation of the dose deposition for the entire treatment, which is necessary to compute the Dose Volume Histograms (DVH's) that are used to evaluate the treatment quality (cf. chapter 3).

Following this, we started working on 3D motion models and developed the method presented in chapter 5 to use 2D MRI dynamic sequences to drive 3D motion models and reproduce continuously a 3D breathing motion that is compatible with the motion observed on the 2D MRI frames.

Then in chapter 6, we add a step to our method to improve the precision of the reproduced motion by combining multiple deformation fields to adjust locally the resulting deformation, and better match the observed motion.

We finally conclude in chapter 7 by discussing the scope of possible uses of our methods in clinical practice, their limitations and the potential of real time uses of online 2D MRI acquisition in general.

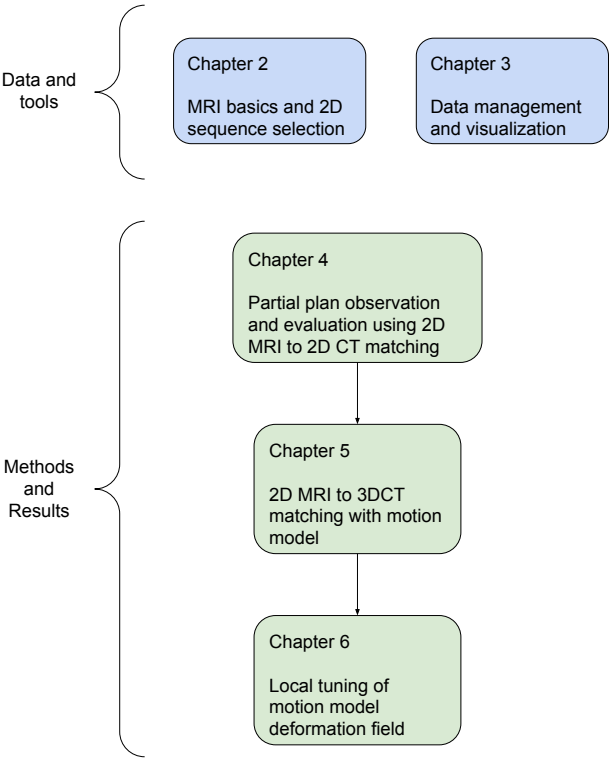


Figure 1.8: Flow chart of the thesis chapters with the main topics they cover.

Chapter 2

Magnetic Resonance Imaging and Sequence Selection

2.1 Introduction

The development of hybrid hardware combining MRI and linear accelerators motivated our research. This chapter contains the basic principles of magnetic resonance imaging (MRI) and basic information about the specific sequence that is used for this thesis, which is the Balanced Steady State Free Precession sequence (BSSFP). We restricted our explanations to the basic principles to cover how an image can be formed using the magnetic resonance properties of tissues. We let the technological details to the references related to MRI.

2.2 Magnetic Resonance Imaging General Principles

Organic tissues are principally composed of Carbon, Oxygen and Hydrogen which counts for about 93 % of human mass¹. Hydrogen nuclei are everywhere in the human body due to their abundance in water

¹https://en.wikipedia.org/wiki/Composition_of_the_human_body

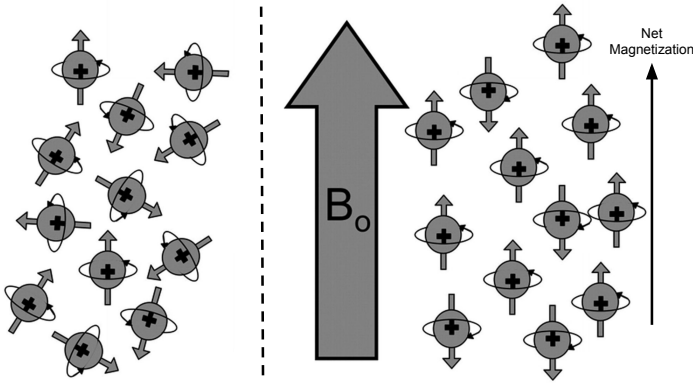


Figure 2.1: Hydrogen nuclei at rest (left) and within an external magnetic field B_0 (right). After being put in the field, the net macroscopic magnetization appears and is parallel to the B_0 field. [85]

and every lipid that compose our cell membranes. They possess a small magnetic moment called nuclear spin. It can be represented as a small dipole centered on the nuclei. In common situation, the net magnetic field created by all Hydrogen spins is null because their directions are randomly distributed. Once put inside an external magnetic field, usually called B_0 in MRI, all these little magnetic spins align with the B_0 field, either parallel or anti-parallel. The parallel state is a lower energy state than the anti-parallel state, which result in a slightly higher proportion of parallel ones and a net magnetization parallel to the B_0 field. [Figure 2.1]

Additionally to their alignment, a small dipole placed in a external field rotates around its axis at a frequency called the Larmor frequency or precession frequency $\omega_0 = \gamma B_0$ dependent of the B_0 field intensity and of the gyromagnetic ratio γ of the nuclei (42.577 MHz/T for hydrogen) [Figure 2.2]. With the precession, the magnetic moment can be splitted into 2 orthogonal components, the longitudinal component perfectly aligned with the B_0 field, and the transverse component, perpendicular to the longitudinal and rotating at the Larmor frequency. But as they do not rotate in phase, the sum of all protons transverse magnetization results in a null macroscopic transverse magnetization.

The magnetic resonance is the energetic interaction between spins

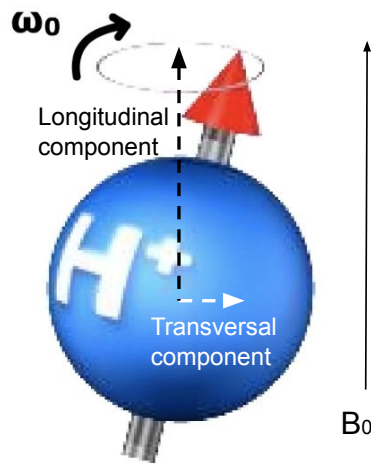


Figure 2.2: Representation of a spinning hydrogen nuclei in a magnetic field B_0 . Its magnetic moment can be split into an immobile longitudinal component and a transversal component rotating at the larmor frequency ω_0 . [89]

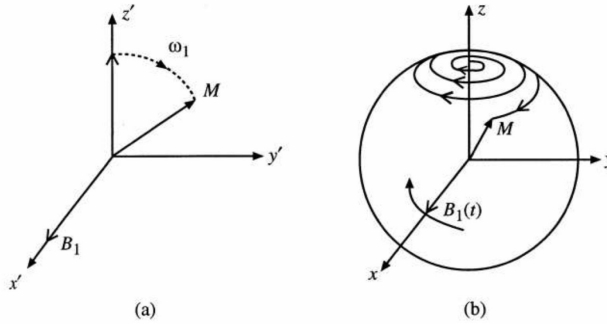


Figure 2.3: Under an external RF pulse, the net magnetization can be represented as a flipping vector in a rotating frame (x' , y' , z') which rotates around z' at the Larmor frequency ω_0 (a) or as a vector spiraling down towards the XY plane, slowly losing its longitudinal part and building up its transversal part as spins get in phase (b). [84]

rotating at a specific frequency with an electromagnetic signal of the same frequency called the RF pulse, emitted inside the scanner. This resonance is also called excitation because it gives energy to some of the hydrogen nuclei which pass from the parallel state (lower energy) to the antiparallel state (higher energy). It modifies the ratio of parallel / antiparallel nuclei and changes the direction of the net magnetization. The longer the RF pulse is applied, the more the ratio will decrease. Additionally, the excitation will cause the rotating spins to get in phase, which will result in a transverse magnetization appearing and rotating in the plane perpendicular to B_0 .

The macroscopic magnetization can be represented by a vector spiraling down towards the XY plane or simply flipping in a frame or reference rotating with the transverse magnetization at ω_0 [Figure 2.3]. The RF pulse can be designed to flip the magnetization to a specific angle called the flip angle. For example after an 90 degrees excitation, the longitudinal magnetization is null and the transverse magnetization is maximum.

What interests us to create an image is what comes after the RF pulse is stopped: the relaxation. The relaxation is the inverse process

Tissue	T1 (ms)	T2 (ms)
Liver	500	40
Water	4000	2000
Fat	250	70
Blood vessels	1400	200
Cortical Bone	200	10

Table 2.1: Examples of T1 and T2 of different tissues in a 1.5T magnetic field.

of the excitation. It starts as soon as the RF pulses is stopped, when no more energy is given to the nuclei. The macroscopic magnetization will start spiraling up again to tend to its resting state as it was before the excitation. The longitudinal magnetization is brought back parallel to B_0 and the transverse magnetization decays because spins get out of phase again. This relaxation process is described using two different time:

- The T1 is the time necessary for the longitudinal magnetization to get back to 63% of its rest value.
- The T2 is the time necessary for the transverse magnetization to decay to 37% of its maximum value.

The important part is the following: T1 and T2 are not the same for each type of tissue [Table 2.1]. This difference in T1 and T2 relaxation times is what can be used to create an image.

During the relaxation, the transverse magnetization is still precessing at the resonance frequency even if it's amplitude is decaying due to spins getting out of phase. It creates in a receiving coils an oscillating current that also decreases in amplitude with the transverse magnetization. It is called the Free Induction Decay (FID) and its envelop is decaying proportionally to T2 [Figure 2.4].

The FID is the signal that can be measured to create the image intensities. By choosing the time at which the FID signal is measured, it is possible to differentiate tissues as shown in figure. The time between the RF pulse and the measure is called Echo Time (TE) and the time between two RF pulses is called Repetition Time (TR).

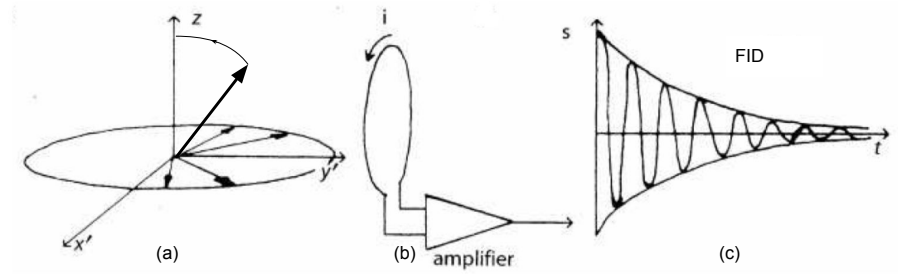


Figure 2.4: Representation of the signal creation. During relaxation spins dephase as represented by small vectors in the plane $x'y'$ and the transverse magnetization decays (a). As the net magnetization is still rotating around Z , it induces a oscillating periodic signal in a receiving coil (b). This signal called the FID signal decrease in amplitude with the transverse magnetization (c). [84]

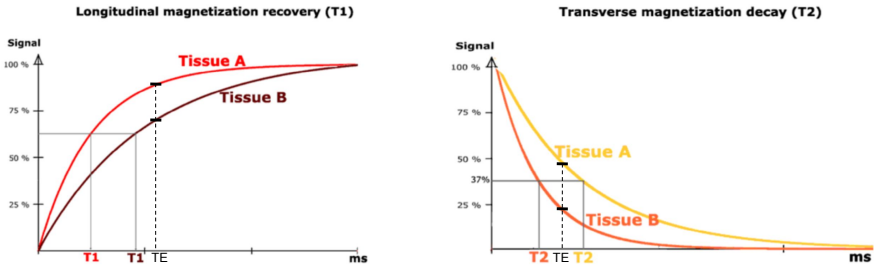


Figure 2.5: Representation of longitudinal and transverse relaxation of two tissues with their respective $T1$ and $T2$. We can see that if the signal is measure after the time TE , the two tissue can be differentiated. [89]

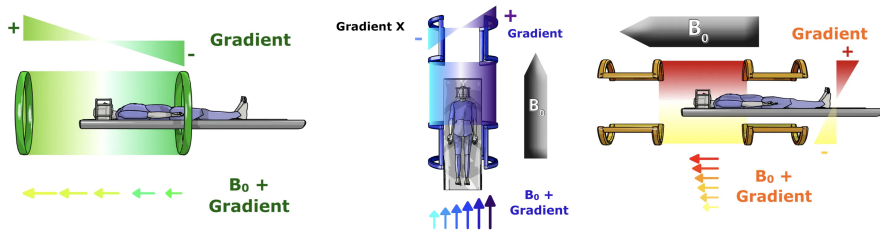


Figure 2.6: Representation of the gradient coils and the three different gradient directions. These gradients can be added to the B_0 field to modify the precession frequency of hydrogen nuclei in their respective direction. [89]

The issue is that simply measuring this signal is not enough if we don't know from which part of the body it comes from. If the entire body is excited, the signal will be the sum of all tissue signals and come from everywhere. It will not be possible to sort out which part of the signal comes from which location in the body. To only get information from one part of the body at the time, magnetic field gradient are created using additional coils for each of the 3 perpendicular spatial direction [Figure 2.6]. It results in a slight linear variation of magnetic field and precession frequency for each direction. Using this, it is possible to apply the excitation to a specific part of the patient's body by using an RF pulse with the frequency corresponding to this area.

MRI parameters such as magnetic field gradient, RF pulses, TR, TE must be combined and tuned in a certain order (that is why it called an MRI *sequence*) to find the best compromise between signal to noise ratio, contrast and acquisition speed. As our objective is to follow the breathing pattern of a patient with eventual irregularities, the acquisition speed was the priority for our application. Different methods now exists to speed up the acquisitions such as parallel imaging [26] or partial k-space filling [20]. The sequence we finally chose is called Balanced Steady State Free Precession (BSSFP) and is explained in the next section.

2.3 Our Sequence Choice

2.3.1 Gradient Echo Family

The BSSFP sequence is part of the gradient echo sequences family, meaning that the flip angle is usually less than 90 degrees. By using a lower flip angle than 90 degrees, the longitudinal magnetization recovers faster, making it possible to use shorter TR and TE to accelerate the acquisition. It was developed in the early 2000 to serve as cardiac imaging.

In gradient echo sequences using TR shorter than T2, the transverse magnetization has not completely faded before the next RF pulse is sent. This can be handled in two ways:

- Spoil the residual transverse magnetization by forcing a dephasing of the spins before the next RF pulse.
- Add nothing special and sent the RF pulse while the residual transverse magnetization is still present.

The first option is a Spoiled Gradient-Echo sequence and it gives a T1 weighted contrast. The second one is the BSSFP and gives a T2/T1 contrast. The contrast of the BSSFP is better to see liver tumor or liver blood vessels [Figure 2.7], but they come with banding artifacts (cf. section 2.3.3). As we worked with patient treated for liver tumors, we preferred the BSSFP despite the artifacts.

2.3.2 Balanced Steady State Free Precession

In steady state sequences the transverse magnetization has not completely faded after the first TR, meaning that the net magnetization is still tilted of a residual angle when the second pulse arrives. The flip angle has to be added to this residual angle at each TR [Figure 2.8]. But as the transverse magnetization follows an exponential decreasing curve and decays faster initially, at one point the steady state is reached where the transverse magnetization decreases after each pulse by the same amount as what it gains from each pulse.

The TE is usually chosen equal as TR/2, meaning the measure is taken exactly between 2 pulses. The *balanced* comes from the fact that

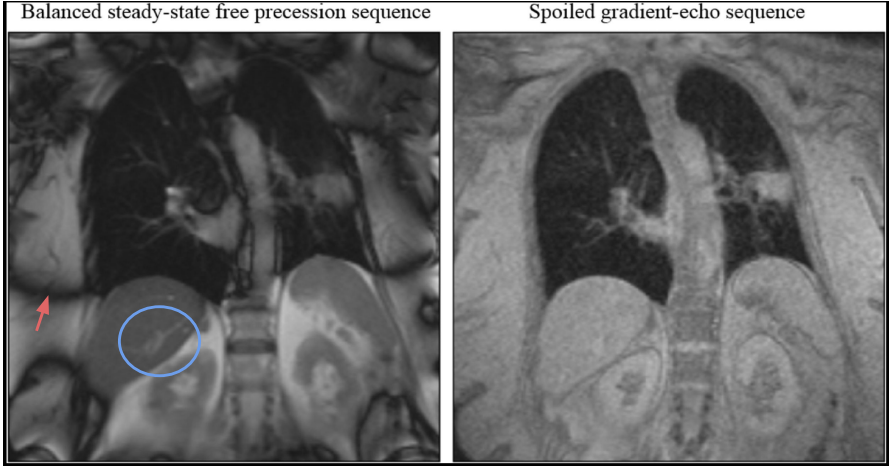


Figure 2.7: Example of slices from BSSFP and Gradient-Echo sequences. We can see the contrast in the liver is better with the BSSFP (blue circle), but it also brings banding artifacts (dark band pointed by the red arrow).[10]

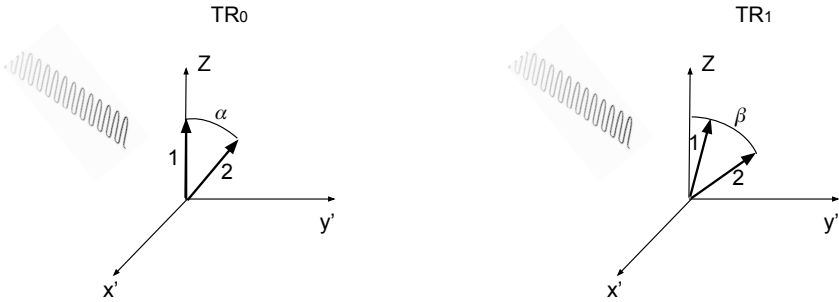


Figure 2.8: Representation of the first two TR and flip angles in a rotating frame of reference for a steady state sequence. As the magnetization is not yet completely parallel to Z before the next pulse arrives, the resulting angle β after the second pulse is bigger than the angle α after the first pulse.

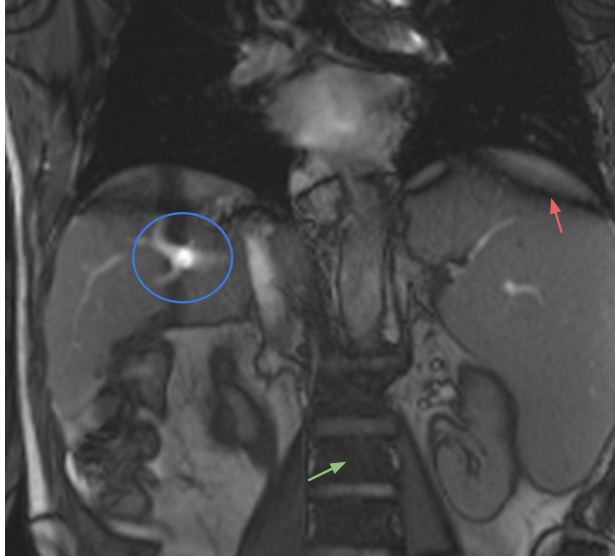


Figure 2.9: Example of coronal slice acquired with a BSSFP sequence. We can see that the blood vessels appear brighter than the surrounding liver tissue (blue circle), that the bones appear dark (green arrow) and that there is a banding artifact around the left diaphragmatic dome (dark band showed by the red arrow).

each gradient is inverted after TE. Depending on the constructor, the sequence can have different name and variation. (Balanced FFE in Phillips scanners and TrueFisp in Siemens scanners.) The BSSFP sequence gives a contrast proportional to the $T2 / T1$ ratio, meaning that for equivalent $T1$, the longer the $T2$ the brighter tissues will appear and for equivalent $T2$, the longer the $T1$ the darker tissues will appear. Liquids like blood in vessels will appear bright and tissues with really short $T2$ like bones will appear dark [Table 2.1] [Figure 2.9].

2.3.3 Banding Artifacts

The downside of this sequence is that it can create *banding artifacts* that are dark bands that can appear close to tissue interfaces [Figure 2.9]. They are due to magnetic field gradient not always being perfectly

balanced everywhere due to slight inhomogeneities in the gradients [17, 76, 90]. It is difficult to completely avoid these artefacts, but by adding a frequency offset in the pulse and the corresponding offset in the gradient intensities, the artifacts can be spatially displaced [106, 4, 52]. We used this frequency offset in our patient study to move artifacts as far as possible from tumor or organ edges. This way, we were able to use our border tracking method (cf. chapter 5) despite the artifacts being present in most patient acquisitions.

2.3.4 Specific Absorption Rate Limitations and Technological Progress

One last thing to discuss about MRI is the Specific Absorption Rate (SAR). While MRI does not irradiate the tissues to create an image, it can still have an impact on tissue that must be controlled. When tissues are excited by RF pulses, a transfer of energy occurs from the RF pulse to the tissue, which can cause heating and damage the cells if it exceeds a certain threshold. The SAR is a measure of the quantity of electromagnetic energy given to the tissue in W/Kg. In some cases with ultra fast imaging like we use here with really short TR, too much RF pulses are used in a short period of time and the SAR limit has to be considered. Each manufacturer of MRI scanner must include safety rules in their software to prevent the user to exceed the SAR limit which are defined in the international standards for MR equipment safety ².

MRI is an imaging modality in constant amelioration. The different hardware and software parts keep getting better and better as new technologies and research results emerge and this should continue to improve in the near future. The images we use in this thesis are far from the state of the art options developed in research or even in the last version of commercially available scanners, but we used what was available for us.

²<http://mriquestions.com/sar-limits.html>

Chapter 3

Data management and visualization/analysis tool

3.1 Introduction

Data acquisition, collection and manipulation are important and often underestimated parts of this kind of research project. Once the necessary data has been identified, and if it turns out to be possible to acquire them, it can be time consuming to acquire and format the data in such a way that they can be processed and studied.

If patient data is required and that the type of data is not available yet, a prospective patient study has to be approved by the ethic committee of an hospital. To start the data acquisition, patients have to be informed about the study goal and potential risks or side effects and agree to participate. This can also take time depending on the type of data, the number of available patients and the number of patients willing to participate. It is easier and faster with retrospective studies that relies on already available data, but as this technology is recent and the BSSFP sequence was only used for cardiac imaging, no such data were available.

For this project we gathered more than 50 000 2D MRI images, 260 3DCT images, treatment plans, contours, deformation fields, dose prescription etc. It was an outstanding data management challenge. This is why I chose to dedicate a chapter to this topic to explain the different data types and formats that were necessary for our research

projects, as well as the different software tools we used and the Graphical User Interface (GUI) that we developed ourselves to achieve our goals.

A first version of the GUI was presented at the U-CRC symposium in Brussels in 2017 [22] and then an updated version at the MRinRT annual symposium in 2018 [23].

3.2 Data type and acquisition

3.2.1 Magnetic Resonance Imaging Data

In 2016 when we defined the research objectives, we started testing Magnetic Resonance Imaging (MRI) sequences on volunteers to see if it was possible to observe the breathing motion of a patient. Based on suggestions of the Pr. Metens of the Université Libre de Bruxelles, we used *Balanced Steady State Free Precession* sequences (BSSFP). The particularities of this sequence are described in chapter 2. With a couple of test sessions on volunteers, we had selected the following set of plane configurations to acquire on patients.

- 2 orthogonal planes in sagittal and coronal direction
- 1 single plane higher resolution in sagittal or coronal direction
- 3 parallel planes in sagittal or coronal direction
- 5 parallel planes in sagittal or coronal direction
- 5 parallel planes with big inter plane space in sagittal or coronal direction

Note that when more than a single plane is acquired, the multiple planes are not acquired at the same exact time. They are acquired successively until having all the planes (5 at most) and then the loop starts again at the first plane. Given that the images coming from the 5 parallel planes configuration seemed of poor quality and to reduce the acquisition time for patient comfort, we finally decided to select three configurations of planes for acquisition of two minutes each. We chose in priority the two orthogonal planes, a single plane of higher resolution in the sagittal direction and the three parallel planes also in the sagittal direction [Figure 3.1 and 3.2]. For some patients, the two orthogonal planes sequence

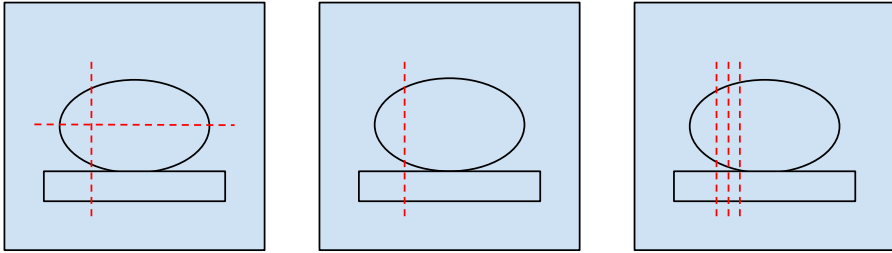


Figure 3.1: Schematic representation of the transversal view for a patient on a table with the MRI planes positions in the three selected configuration. Left: Two orthogonal sagittal and coronal planes. Center: A single plane in sagittal direction. Right: Three parallel planes in sagittal direction.

was acquired two times, with and without contrast agent. Here below are the main characteristics and MRI parameters for each of the three configurations:

1. Single slice in sagittal or coronal plane:
 - 3.16 Hz for 380 slices in 2 minutes
 - TE: 1.41, TR: 3.23, 208x204 pixels of 1.6x1.6x7 mm
2. Two interleaved coronal and sagittal slices:
 - 1.83 Hz for both orientation (3.66 Hz in total), 440 slices (2 x 220) in 2 minutes
 - TE: 1.39, TR: 3.16, 188x192 pixels of 1.82x1.82x7 mm
3. Three contiguous slices in sagittal or coronal plane:
 - 1.5 Hz for the 3 slices (4.5 Hz in total), 540 slices (3 x 180) in 2 minutes
 - TE: 1.33, TR: 3.01, 126x128 pixels of 2.5x2.5x7 mm

Our patient study gathered 25 patients over 3 years. These patients were treated for primary (hepatocarcinoma) or secondary (metastasis) liver tumors by radiotherapy in the *Cliniques Universitaires St Luc*. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, approved by our local ethics committee (B403201628906). Informed consent was obtained from all participants before the trial.

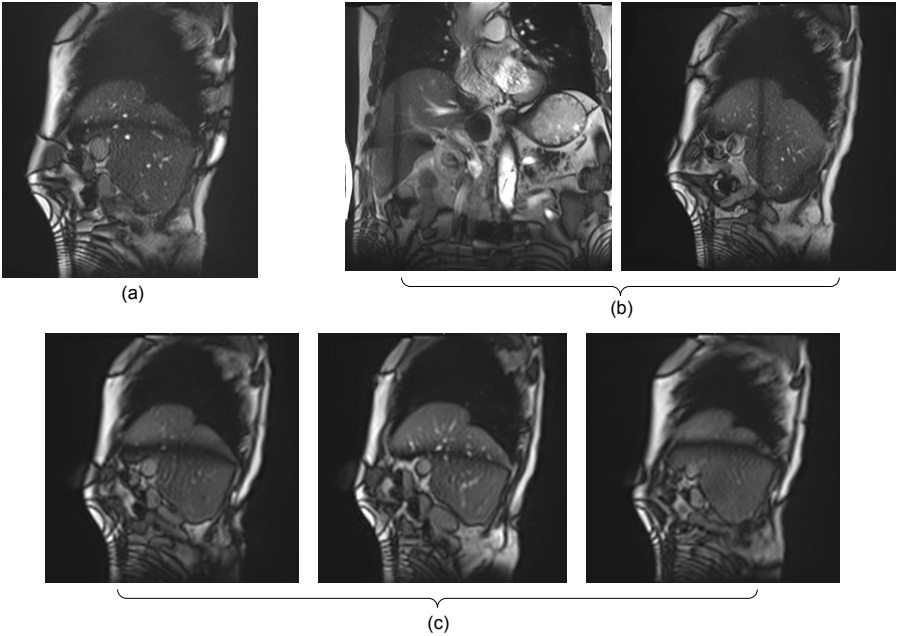


Figure 3.2: Example of slices for the 3 geometric configurations: single sagittal plane (a), interleaved coronal and sagittal planes (b), and three parallel sagittal planes of lower resolution (c).

Our tests on volunteers were made on a Phillips MRI scanner, but for most of our patients the acquisition ended up being on a Siemens scanner (Skyra 3 Tesla model), so the equivalent sequence had to be tuned for this new scanner of another constructor.

As most medical image data, MRI image data are stored in the hospital in DICOM format. DICOM is the international standard to transmit, store and display medical imaging information¹.

3.2.2 Computed Tomography

Computed Tomography (CT) images are images where pixels are represented in a dimensionless unit called the Hounsfield Units (HU). HU are proportional to the attenuation of x-rays when they pass through tissues, which is proportional to the tissue density. As treatment photons or protons also interact with tissues in proportion to the tissue density, it is possible to compute from the HU the energy attenuation that they undergo while passing through the tissues, and therefore the delivered dose. 3DCT images are then necessary to prepare treatment plans with the 3D information and compute photon or proton doses. As the patient in our study are treated with radiotherapy for liver tumors, a 4DCT is acquired in the standard treatment pipeline they follow. A 4DCT is a small set of 3DCT images (usually 10 images) representing multiple time steps of one breathing period. It is created by acquiring a large number of slices over a couple of minutes while the patient breathes in a trained pattern. The slices are then sorted using an external surrogate signal into N groups called phases (usually 8 or 10 phases, 10 in our data set). In each phase p_n , the slices are then rearranged in space to form a 3DCT image [Figure 3.3].

Each 3DCT phase image has between 160 and 190 slices with a slice thickness of 2 mm where each slice has 512x512 pixels of pixel spacing of 1.074 mm in each direction. Computed tomography image data are also gathered from the hospital in DICOM format.

¹<https://www.dicomstandard.org/>



Figure 3.3: Example of slices extracted from three different phases of a 4DCT but at the same location. The breathing motion happening between the phases is clearly visible at the lung/liver interface (red circles).

3.2.3 Deformation fields and mid position image

After the 4DCT acquisition, deformation fields are computed from every other phase of the 4DCT to a reference phase using non-rigid registration (cf. section 3.5). These deformation fields are saved to be used later (cf. motion model in chapter 5). They are also used to compute the average deformation of all the fields from each phase to the reference phase. This gives an average position called the mid position [105]. Then, every phase image is deformed on the mid position where the median is computed to create the mid position image [Figure 3.4]. Is it an image which represents the average position over the breathing period but is not blurred, because the averaging is made on the deformation fields and not on the images themselves. On top of this, the median over all the deformed phases allows to remove noise and eventual reconstruction artefacts of the 4DCT.

The mid position image (midP 3DCT) has the same size and resolution as the phases in the 4DCT and is also saved in DICOM format after being created, as well as the deformation fields.

3.2.4 Protontherapy Treatment Plans

For the results shown in chapter 4, treatment plans have been generated with the RayStation 6 (Raysearch) by optimizing a single field uniform

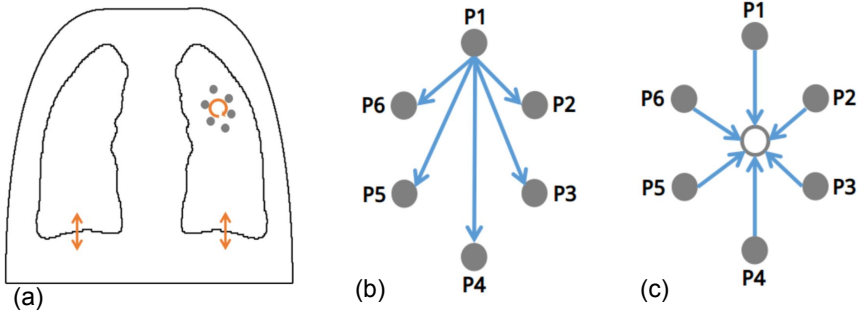


Figure 3.4: The tumor motion is schematically represented by the hysteresis formed by the tumor position (gray circles) at each phase of the 4DCT (a). Deformation fields (blue vectors) are generated using registration between the first phase (P1) and all others phases (b). Then, all phases can be deformed to the average motion called the Mid-Position where the MidP-CT image is then created by taking the median in each voxel of all deformed phases (c).

dose (SFUD) on beam specific PTVs to take into account range variations due to motion, setup errors, and HU conversion uncertainties. The beam angles have been selected exactly perpendicular or parallel to the dynamic MRI acquisitions available [Figure 3.5]. The detailed Pencil Beam Scanning (PBS) plan containing for each spot of each beam the position and the delivery timing is computed by ScanAlgo software (IBA SA Louvain-la-Neuve).

3.2.5 Contours

The contours on the CT images comes from the standard patient treatment pipeline and were made by medical doctors. They contains the liver, organs at risk around the liver and the tumor.

The contours of the PTV and CTV on the MRI dynamic sequence were made by me using the software MIM² under the supervision of a medical doctor [Figure 3.6].

Contours comes from files in the standard format for contours which

²<https://www.mimsoftware.com/>

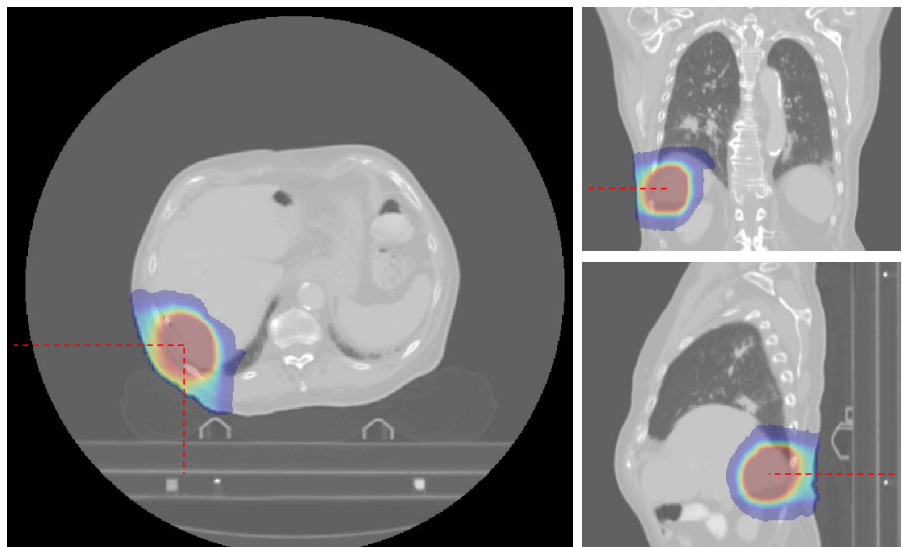


Figure 3.5: Example of planned dose distribution and chosen beam angles, parallel to the interleaved orthogonal coronal and sagittal MRI planes.

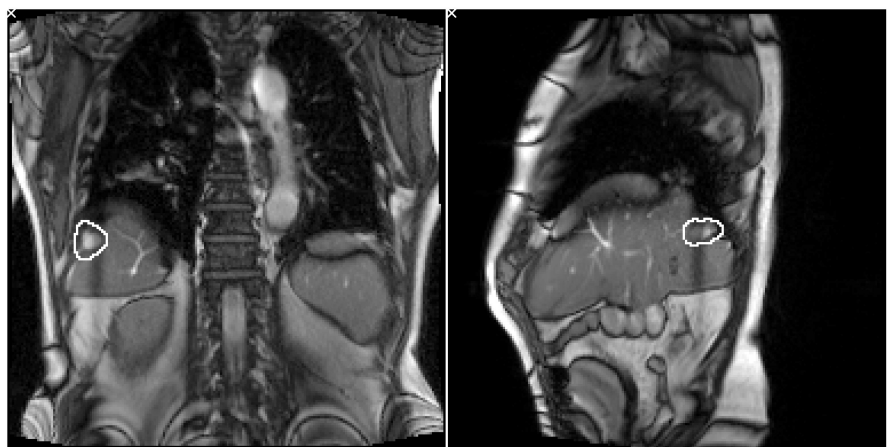


Figure 3.6: Example of PTV contour (white line) on a coronal (left) and a sagittal (right) MRI slices.

is dicom rtstruct. It contains for each contour the name of the contour and the list of 3D points $p_i = (x_i, y_i, z_i)$ that form the mesh of the 3D contour split by slice in the coordinate system of the image on which they were drawn.

3.3 Data preparation and linking step

Data dictionary creation

Before it can be opened in the GUI, all this data has to pass to an initial preparation script to uniformize all the coordinate systems between the different data sources and be put in a format better suited to our needs. This script will read all the data of a particular patient from their original files and create a global dictionary in which all the data are stored efficiently and can be accessed using dictionary keys. Under this format, a data can be accessed using a series of keys to navigate inside the data structure. This dictionary can be easily stored and loaded again when necessary. It is limited in size by the RAM memory available, but usually it is not an issue. This initial preparation script is not part of the GUI yet and not really user friendly.

Registering dynamic MRI with 4DCT

To find which area in the 4DCT corresponds to the same area as the MRI planes, the MRI dynamic sequences have to be registered on the 4DCT. This means registering spatially a 3D CT video on a 2D MRI video, which is not trivial. For our study and our 25 patients, we did it manually by looking at the two video side by side and scrolling through the 4DCT data in the spatial dimension perpendicular to the MRI planes. By observing the videos side by side, which also showed the breathing motion, it was possible to select the CT slice position which seemed to contain the most similar anatomical structures as what is seen on the MRI. Then, using stationary structures visible on both sequences, a set of 3 to 5 pair of reference points were selected by a medical doctor on both image modalities [Figure 3.7]. The average difference in 3D coordinates for this set of point pairs is then used as rigid registration difference.

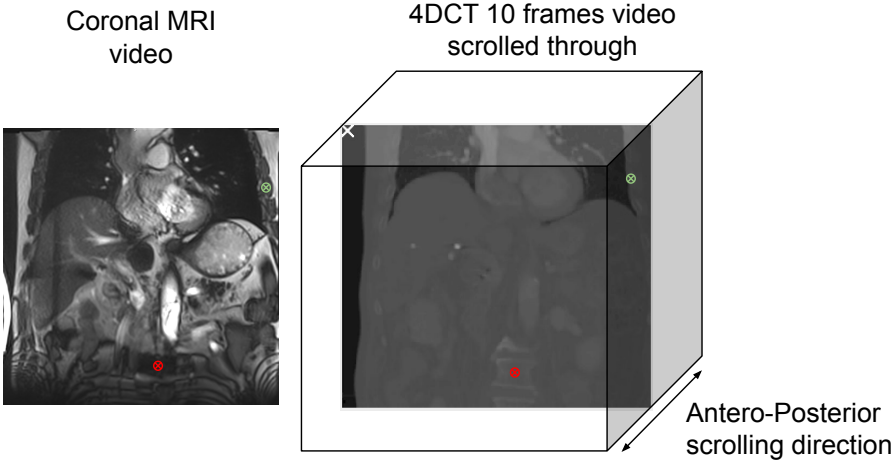


Figure 3.7: Example of manual MR-CT spatial registration by similarity observation and selection of registration point pairs. The 4DCT data is scrolled through in the direction perpendicular to the MRI slice, until the most similar slice is found by a medical doctor observing the anatomical structures. Then, a set of points pair are selected as registration points and their coordinates are saved (Red and green crosses).

Having this, every information given in CT coordinates such as treatment plans or contours, can now also be observed on the MRI images simply by shifting the 3D coordinates using the computed difference. This manual multi-modal and multi-dimensional 2D + time MRI with 3D + time CT rigid registration could probably be automated by performing a multi-modal rigid registration on the stationary parts of both time sequences but we did not try for this work.

To measure and compare the breathing motion with the method described in Chapter 5, the CT slices corresponding to the MRI area must be extracted from the 4DCT. As the MRI slices are 8 mm thick and the CT slices only 1 mm thick, an aggregate of several CT slices is used to represent roughly the same thickness of tissue. Additional slices are added on both sides around the selected slice (the slice chosen by the medical doctor) to approach without exceeding the thickness of the MRI slice. For example with MRI slices of 8 mm, an odd number of 7 CT slices will be chosen. The selected slice and 3 additional slices to each side to finally extract 7 mm thick of tissues [Figure 3.8]. From these 7 slices, an average slice is computed by taking for each pixel the average value of the 7 pixels in the direction of the thickness.

Linking MRI series with PBS spot timings

After passing to the ScanAlgo algorithm mentioned previously, each spot is given the time at which it will be shot and its duration (the duration is proportional to the quantity of protons to deliver at this position). Then, by choosing a starting time for the treatment delivery, each spot can be associated with the corresponding MRI frame throughout the treatment and MRI image series.

3.4 Data visualization and motion tracking GUI

Early during this thesis we realized there was not free software tools to track and measure easily motion amplitudes on time image series. We then decided to develop it ourselves and started a Graphical User Interface (GUI) development in the interpreted programming language

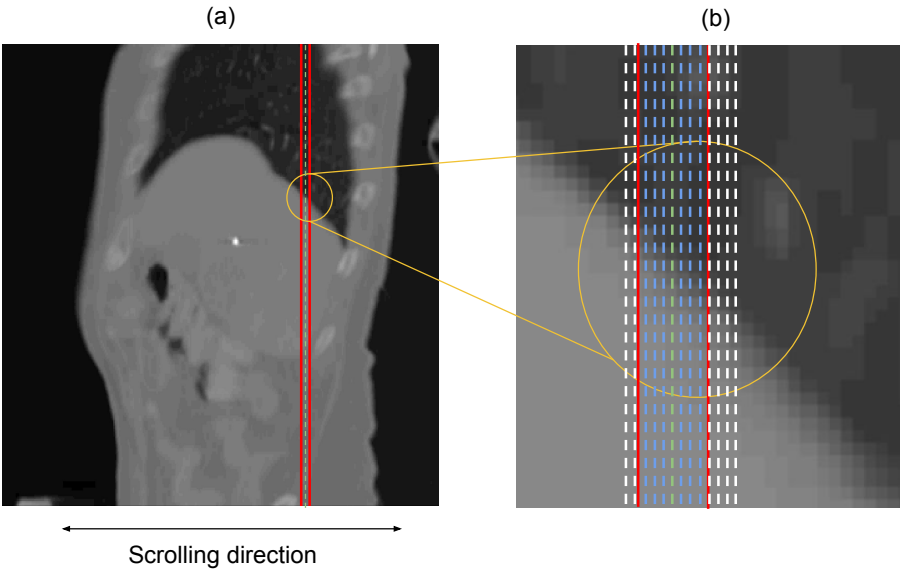


Figure 3.8: Example of CT slice selection resulting from slice thickness differences between the MRI and the CT slices. The coronal MRI slice thickness is shown by red lines on a sagittal CT view (a). The slice selected by the doctor is shown by the green dotted line in between the red lines. On the zoomed view (b), the available CT slice positions are shown by vertical dotted lines. With the selected green dotted slice, 3 additional slices are selected on each side (in blue) to get roughly the same slice thickness as the MRI while keeping the selected slice in the center or the thickness.

Python³ using the QT⁴ graphical library for the graphical parts. When the software is launched, it will ask for a data dictionary (see section 3.3).

Dynamic image series visualization

The main feature of the tool is to show 2D time image series in video to observe and track the breathing induced motion. One or more dynamic sequences present in the data can be displayed and the video flux can be accelerated, slowed or paused.

It is possible to change the displayed intensities of the images using the usual contrast stretching, depending on what type of tissue is observed. The principle is to redefine the range of pixel values which are represented in grey levels in the displayed image by choosing a lower and upper threshold. Everything under the lower threshold of the range is put to black, everything over the upper threshold is put to white and everything in between is mapped in grey levels linearly. This way the region of interest in the image can be represented using the full spectrum of greys [Figure 3.9]. It is done by using the right clic and moving the mouse over the image.

Interface tracking using Navigators/Trackers

Trackers, also called navigators in this tool are small lines placed on interfaces between tissues or between tissue and air. They will automatically track the interface position for each new frame of the image series using the image processing pipeline described in chapter 5. They are designed to be placed in the direction of the motion, as perpendicular as possible to the interface they track [Figure 3.10]. They can be placed using a simple press-move-release gesture with the mouse left clic. The left clic defines the first point of the tracker, and the release of the button defines the second point. If the image series is available in its entirety, the motion can be tracked already for the entire sequence for the sake of convenience during research (It shows directly if there are irregularities in the breathing pattern or if the tracker has an issue.). In this case, the current frame position in time is shown by a vertical dotted line [Figure

³<https://www.python.org/>

⁴<https://doc.qt.io/qt-5/>

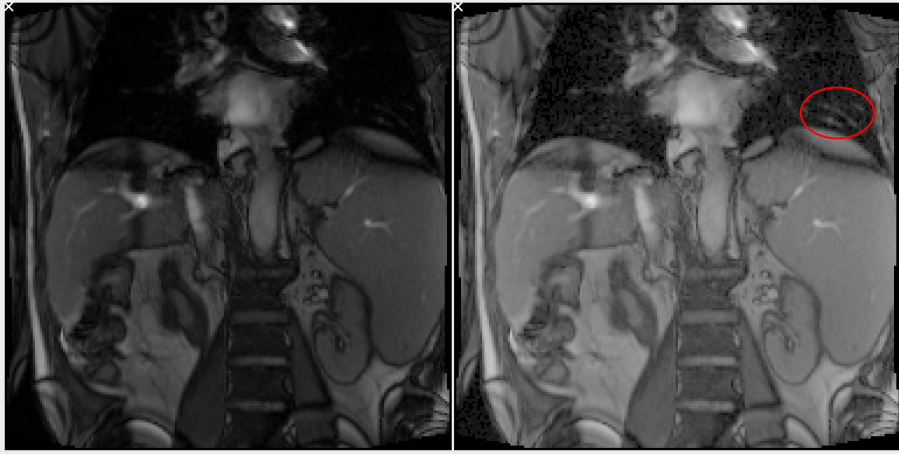


Figure 3.9: Example of contrast stretching to highlight the lung vessels (red circle).

3.10].

I also implemented other navigator options for different usages:

- Multiple navigators

It is possible to place the same navigator on multiple image series at once, for example to compare the motion of the dynamic MRI series with the extracted slices of the 4DCT corresponding to the same anatomical position. First, the position of the mouse on the image on which the navigator is placed is converted into scanner coordinates. Then, respective position, orientation and pixel spacing of each series is used to place a navigator at the correct position on each image series and start the tracking [Figure 3.11]. This is used to compare the motion of the same anatomical area on multiple image series.

- Fixed Point Navigators and Multiple Fixed Point Navigators

Navigators can also be associated with a fixed point. In this case, the user must first place a fixed point, usually on an immobile

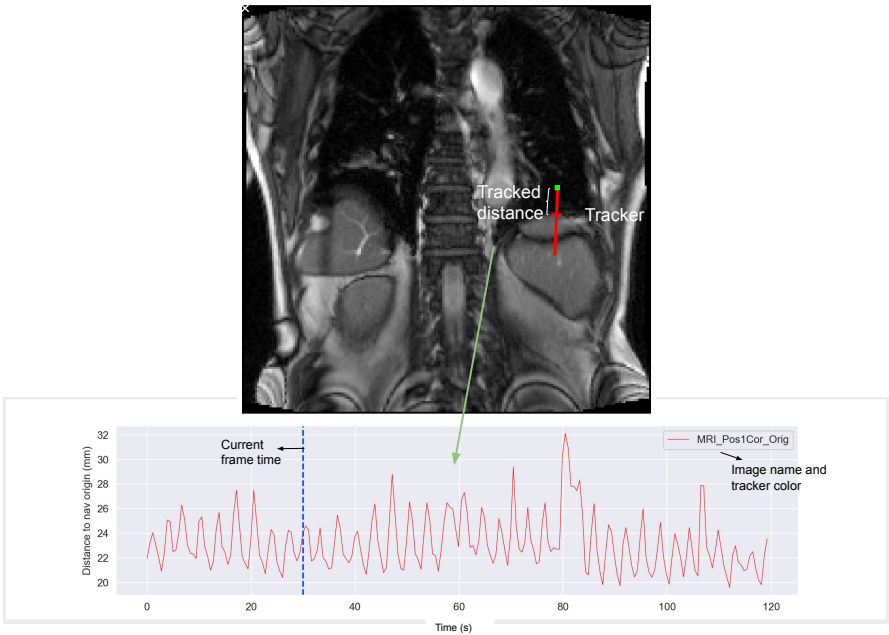


Figure 3.10: Example of tracker placed on the left diaphragmatic dome and the resulting motion signal, given as the distance from the first point of the tracker (green square) to the detected interface. The vertical dotted blue line shows the time of the currently showed frame.

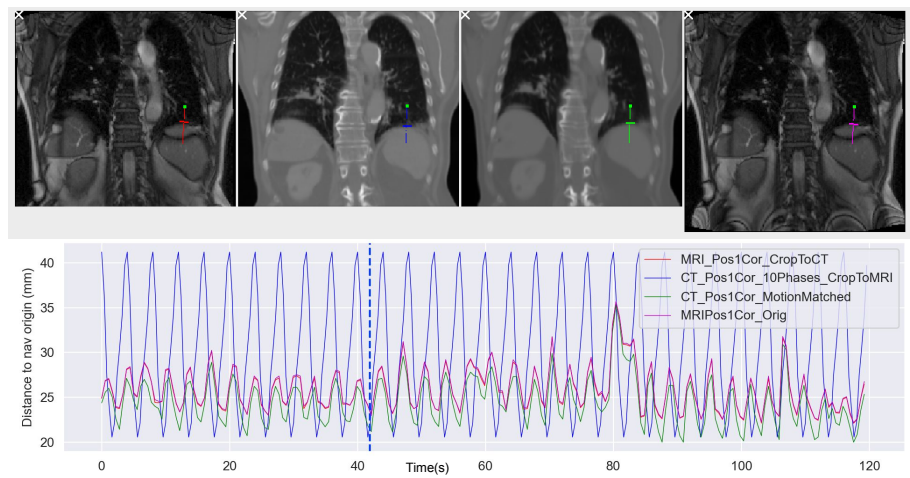


Figure 3.11: Example of multiple navigators placed automatically at the same position on several image series using only one clic-move-release gesture. Each series can have a different size or pixel spacing. The clic and release coordinates on the user’s screen are used to transfer the position in scanner coordinates to every image series and start the tracking.

structure such as a vertebrae. Then, a standard navigator is placed but this time the tracked distance is given as the distance between the detected interface and the fixed point [Figure 3.12]. In practice, both the distances in vertical and horizontal dimensions are computed and used to compute the hypotenuse. This can be used to compare the motion of 2 images series from different time point. For example to compare the motion amplitude of the diaphragm in images series acquired in two different weeks, using the same vertebrae as fixed point. This mode also exist in *Multiple Navigator* version, where the fixed point will be automatically transferred to each opened image series. In the case of interleaved coronal and sagittal slices, if one of the two image orientation does not show an immobile structure, the selected fixed point can be projected from the slice which does on the other slice orientation to allow a motion comparison anyway. The user must simply be careful to compare the correct motion (it might be necessary to only take the vertical or horizontal part of the motion in this case.)

- Save/Import Navigators

Navigators position and resulting tracked motion can be saved to be analysed or compared later (there is not much motion signal comparison options in the tool for now). In this case the navigator ID informations such as the coordinates of the two navigator points, the navigator type or the name of the image series on which it was placed are saved in a txt file, as well as the tracking results containing the timing of each measure in ms and the associated distance between the navigator origin and the tracked interface in mm [Figure 3.13] (and vertical/horizontal distances with the fixed point if there is any).

From these txt files, navigators can also be imported. An imported navigator will copy the ID informations from the txt file but not the tracking results. The tracking will be applied again on the image series on which it was imported. This way it is possible to compare motions at the exact same location later, for example after modifications on the images.

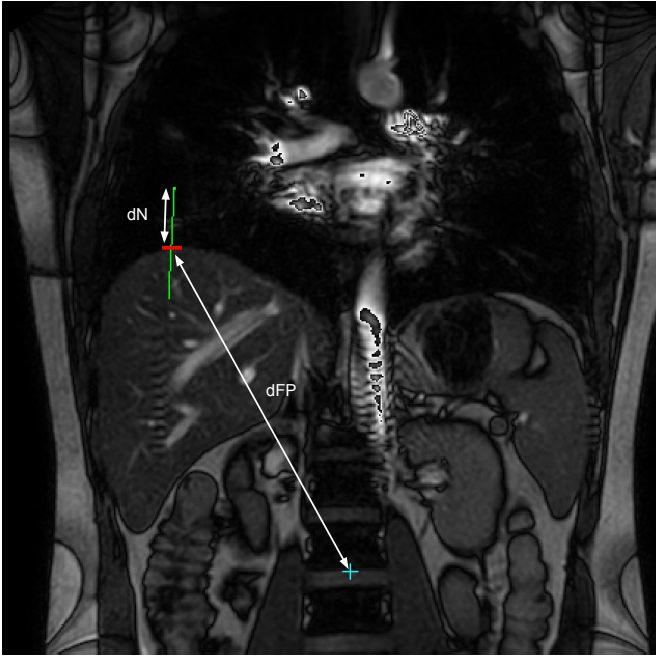


Figure 3.12: Example of fixed point navigator. The user places the fixed point first (blue cross), then the navigator. The resulting distance dFP can then be measure on top of the standard dN .

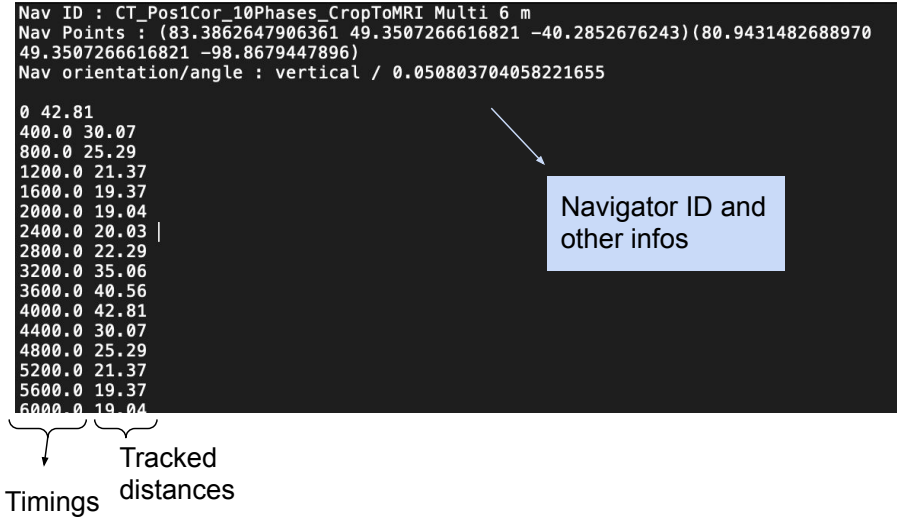


Figure 3.13: Example of saved navigator in txt file. The header gives the navigator name, position and orientation. The data listed below shows the measures and the measure timings.

3D images

While the visualization of 4D images series is not implemented for now, static 3D images can be displayed if available. It is possible to show them in transversal (default), coronal or sagittal direction, and it is possible to scroll through them using the mouse wheel and to add on overlay contours or dose maps [Figure 3.14]

If a 3D image and a 2D dynamic image series are open and if registration points between them are given, it is possible to show the position of the 2D time series in the 3D image [Figure 3.15].

Dose Volume Histograms

If a dose map and contours are available, it is also possible to compute Dose Volume Histograms (DVH). It gives the fraction of the volume (here the part of the image inside a contour), which receive a certain dose. It is an important and commonly used tool in dosimetry because

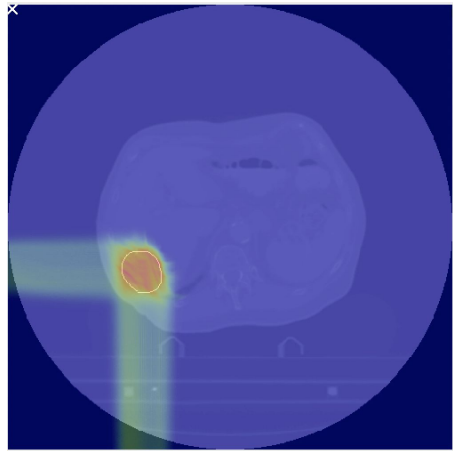


Figure 3.14: Example of 3D image opened in the GUI with a contour (thin white line) and a dose map on overlay.

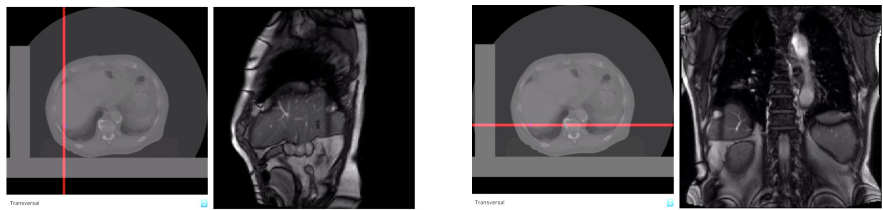


Figure 3.15: Examples of 2D dynamic series positions (sagittal on the left and coronal on the right) shown by a red lines on a 3D transversal image.

it summarises well a 3D dose distribution.

The main GUI screen is split into 3 main pannels: images, motion signals/DVH's, and controls/options as shown in Figure 3.16.

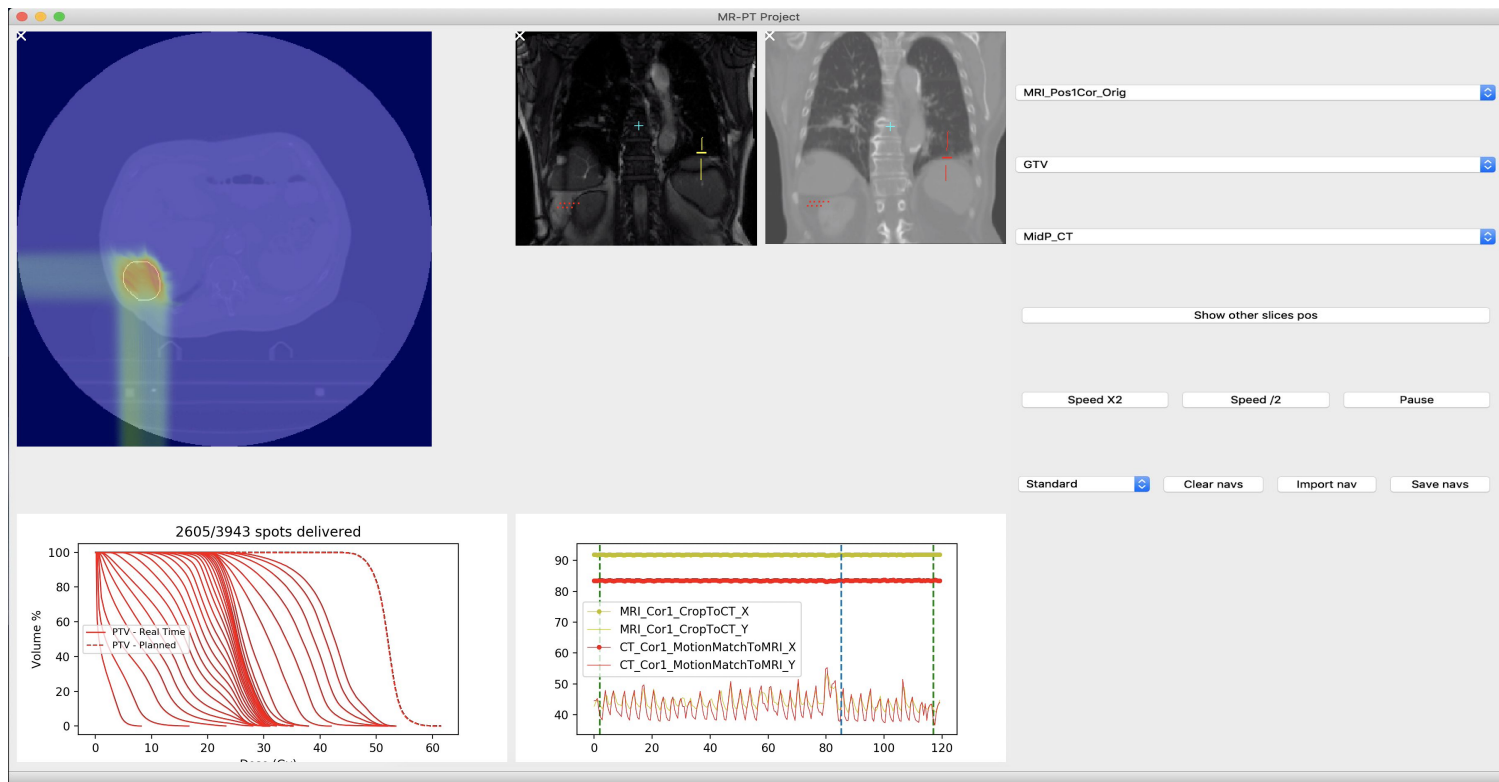


Figure 3.16: Example of the full GUI window. Top left are the image widgets, bottom left the tracked motion and DVH's for the dose, and right is the options/controls panel.

This software has been used for the work presented in this thesis and also by Dr. Geneviève Van Ooteghem to study non-invasive ventilation techniques to mitigate or regulate breathing-related motion during radiotherapy treatment [72, 75, 74].

3.5 OpenReggui and the Morphons algorithm

The non-rigid registration algorithm used to generate the deformation fields between the 4DCT phases, the midP image, and the deformation fields between the 4DCT phases and the midP image was not implemented in Python.

For this we use OpenReggui⁵ which is an open source platforme created for multiple uses in research in radiotherapy and protontherapy. It is made in Matlab⁶ for which a paid license is necessary so it is not ideal. It does however implement an efficient diffeomorphic non-rigid registration algorithm from which we can extract the vector fields we need for our motion model based applications in chapter 5.

Diffeomorphic morphons

The non-rigid registration algorithm we use is called the diffeomorphic morphons. It has been developped by G. Janssens et al. [43]. While the morphons method is interesting and presents advantages to register images with variable contrast, what really interest us here is that this version of the algorithm can give as output two different vector fields: the standard deformation fields or the diffeomorphic velocity fields. It is easy to transform one into the other by applying a computationally efficient transformation as explained by G. Janssens et al.

A diffeomorphism is "*an isomorphism of smooth manifolds. It is an invertible function that maps one differentiable manifold to another such that both the function and its inverse are smooth.*"⁷ A diffeomorphic vector field is then a smooth, invertible and differentiable vector field and its inverse field is also differentiable.

⁵<https://openreggui.org/>

⁶<https://www.mathworks.com/products/matlab.html>

⁷<https://en.wikipedia.org/wiki/Diffeomorphism>

As a result, the velocity field produced by the morphons algorithm can be easily scaled, inverted or summed without the need for complex field composition. These properties will be used to combine multiple velocity fields in chapter 5 and chapter 6. Operations are done with the velocity fields, but to deform an image, it must first be transformed to a standard deformation field. Note that as they are a transformation of one another, I will use the term deformation fields for both in the rest of the thesis.

Chapter 4

Protons Pencil Beam Scanning plans evaluation using 2D cine-MRI

4.1 Introduction

This chapter covers the first research ideas that were investigated using only 2D image series. The rest of the 4DCT volumes were not used, except to extract 2D slices. The work presented in section 4.2 was presented at the U-CRC symposium in Brussels in 2017 [22]. It presents a method to use dynamic MRI to evaluate a proton Pencil Beam Scanning (PBS) delivery by simply checking if the PBS proton spots are shot towards the target or not. The dynamic MRI sequence is used as the ground truth that represent the real anatomy and tumor position over time, including irregular breathing patterns. On this sequence, a proton PBS treatment delivery is simulated. For each spot, we observe using the target contour if the spot is shot towards the target. For the proton spots shot in the direction of the target, the expected range from the treatment plan is used to see if the spot stops inside the target or behind it.

The work of section 4.3 was presented at the 4DWorkshop symposium in Vienna in 2017 [24]. It proposes a way to recompute the range of protons parallel to an MRI slice passing through the slice, while considering the breathing motion observed on the MRI. First, the MRI

sequence, which is used as ground truth again, is spatially registered with the 4DCT of the patient, such that it is possible to extract a small 2D CT video of 10 frames at the same position as the MRI sequence (cf. section 3.7). Then, the diaphragm position is tracked on the dynamic MRI sequence and is compared with the 10 positions present in the 10 frame 2D CT video to find the closest breathing phase in terms of diaphragm position. A non-rigid registration is applied between the closest 2D CT slice and the MRI slice to deform the CT slice and match the ground truth anatomy as best as possible. Finally, the range of protons passing through the slice is recomputed to analyse the effect of the motion on the treatment. It gives a better approximation of the real range of the protons compared to simply using the planning range.

4.2 Simulation and visualization tool for real-time proton PBS treatment delivery

4.2.1 Context and introduction

A possible way to improve external radiation therapy is the use of real-time imaging during treatment. Recently, hybrid imaging-treatment solutions have been developed for standard radiotherapy [55], such as the MR-Linac technology which was first used for online replanning [2]. With such devices, we can expect in the future inter-fraction uses of continuous imaging or even intra-fraction real-time applications. A similar solution is not yet available for protons, mainly because the hardware challenges of building such a machine are more difficult to overcome [70]. But, the possible gain in treatment quality of this kind of hybrid machine is expected to be even higher with protons than with photons, due to the difference in dose deposition profiles and the motion impact on dose distribution [50]. MRI is probably the best choice of modality for such a continuous imaging application, due to its non-irradiant effect, and for its soft tissue contrast performances.

In this context, we developed a tool to visualize and evaluate in real-time proton therapy Pencil Beam Scanning (PBS) treatment plans on dynamic images. This will allow us to compare different treatment strategies, using or not the simultaneous imaging and treatment possibility, and estimate the gain in treatment quality that could be expected

from a PBS-MRI hybrid machine.

4.2.2 Materials and method

The image data we used come from patients treated for primary (hepatocarcinoma) or secondary (metastasis) liver tumors by radiotherapy. For these patients, available data contain:

- 4DCT from which a midP-CT (cf. chapter 3) and a average CT are derived. The average CT is the average 3D image of all the phases of the 4DCT. As breathing motion happens between the 4DCT phases, the average CT is blurred around these areas.
- Dynamic MRI image series of 2 minutes in which interleaved perpendicular planes are acquired, one sagittal and one coronal. The acquisition of the two planes is not simultaneous, meaning the scanner acquires the sagittal slice, then the coronal slice, then the sagittal slice again etc. The acquisition frequency is sufficient to observe breathing motion (between 1.5 and 3 Hz).
- Contours of the target and Organs At Risk (OAR's) delineated by medical doctors on the midP-CT and contours of the target on the MRI dynamic sequences delineated by ourselves, under the supervision of a medical doctor.

Treatment plans have been generated with the RayStation 6 (Raysearch) by optimizing a Single Field Uniform Dose (SFUD) on beam specific PTV's (cf. chapter 1) to take into account range variations due to motion, setup errors, and Hounsfield units (HU) conversion uncertainties. The beam angles have been selected exactly perpendicular or parallel to the dynamic MRI acquisitions available. The detailed PBS plan delivery timing is computed by ScanAlgo software (IBA SA, Louvain-la-Neuve). Then, for each spot of the plan, the expected range is recomputed using the average CT and saved in the list of spots. As for the spot direction evaluation, it would be better to use the MRI slice to recompute the range for the exact current anatomy. But as MRI slices are not suited to compute proton energy loss, we make the assumption that using the average CT to compute the range is, on average, correct.

Once this data is available, it is gathered and the coordinate systems of each data type are uniformized so that each item can be displayed in the right place in relation to the others (The MRI plane positions can be shown in the 3DCT image, the spots coordinates can be shown on both MRI and CT images etc.). This is done in an in-house software coded in Python, using the Qt library for the visualization of images and plan delivery. For this first experiment, the registration of the 2D-MRI images inside the 3DCT or 4DCT was performed manually by a medical doctor by selecting what seemed to be visually the best matching slice of the 4DCT, not based on the target but on the global position of bones, skin and organs.

Then, the plan delivery is simulated by applying it, spot by spot in real-time, on the MRI dynamic sequence [Figure 4.1]. For each delivered spot, the following steps are performed:

- The image corresponding to the timing of the spot is selected in the dynamic sequence for each slice position/orientation of the dynamic sequence.
- For slices perpendicular to the beam, the contours and the spot coordinates are used to check if the spot is shot towards the target or outside of it, regardless the range [Figure 4.2-a].
- For slices parallel to the beam and only for spots passing inside the slice, the contours and the spot coordinates are used to check if the spot passes through the target, stops inside the target or is simply shot outside the target, supposing the range is the expected one [Figure 4.2-b].
- The resulting label (In, Out, or Through) of the spot is recorded to compute statistics and update the visualisation tool accordingly [Figure 4.3]. This is done in terms of number of spots, and also in terms of spot weight, because each spot does not deliver the same dose and missing a heavy spot which delivers a high dose is worse than missing a light one.

Some of the created treatment plans lasted less than the 2 minutes duration of the dynamic MRI sequences. In these cases, random time offsets were added before starting the spots delivery to study the impact of shifting the starting time.

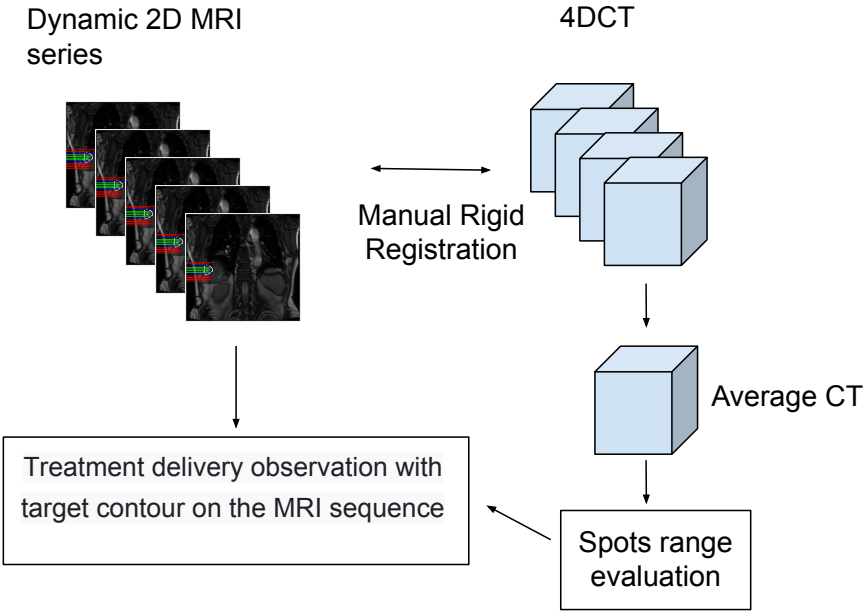


Figure 4.1: Schematic representation of the pipeline. The 4DCT is spatially registered with the dynamic MRI sequence and used to create an average CT on which the proton spot range is evaluated. Then, while the dynamic sequence is running and after choosing a starting time for the treatment delivery, the treatment delivery is observed on the dynamic MRI sequence, where the target contours are available to compute treatment precision statistics.

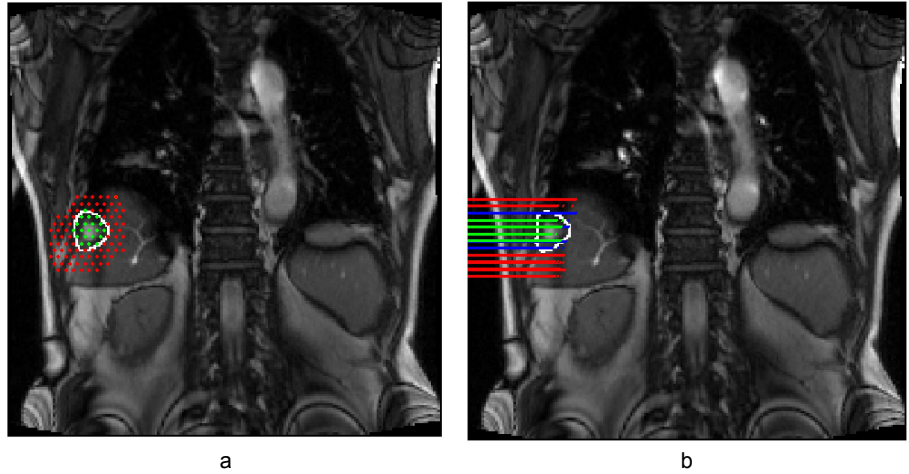


Figure 4.2: Example of beam perpendicular (a) and parallel (b) to the MRI slice. In green the spots shot towards the CTV (white line), in red the spots shot outside the CTV and in blue, only for the parallel case (b), the spot passing through the CTV but stopping behind it.

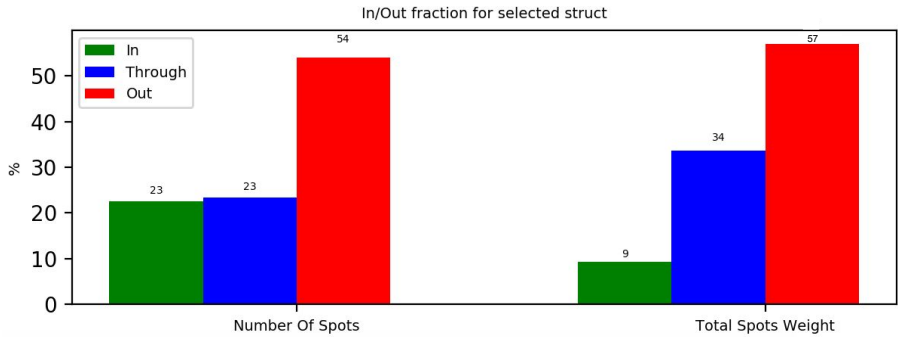


Figure 4.3: Example of spot distribution results after a beam is completely delivered (Coronal slice and parallel beam in this case). On the left part we can see the ratio simply in terms of spot count, and on the right the same results considering the spot weights.

Orientation of the MRI slices	Fraction IN CTV (in # of spots)	Fraction IN CTV (in spot weights)
Sagittal	22% (std=0.6%)	18% (std=0.5%)
Coronal	24% (std = 0.6%)	20% (std=0.8%)

Table 4.1: Average over 10 simulation of the fraction of spots in the CTV in terms of number of spots or weights for the sagittal and coronal planes perpendicular to the MRI planes.

Orientation of the MRI slices	Fraction IN CTV (in spot weights)	Fraction Through CTV (in spot weights)
Sagittal	8-10% (mean = 9%)	22-29 % (mean = 26%)
Coronal	9-11% (mean = 10%)	33-37% (mean = 35%)

Table 4.2: Fraction of spots in and through the CTV in terms of spot weights for the sagittal and coronal planes for the beam parallel to the MRI planes.

4.2.3 Results and discussions

1. Beams perpendicular to the MRI acquisition.

This configuration gives us the fraction of the spots delivered in the CTV direction, as well as this fraction in spot weights. This is done regardless of the range, with 10 different random time shifts for starting the plan delivery [Table 4.1].

2. Beams parallel to the MRI acquisition.

This configuration gives us the fraction of spots delivered through the CTV or which stops inside it, using the expected range computed on the average CT. Again, this is done 10 times with 10 different random time shifts for starting the plan delivery [Table 4.2].

These early results are expected. The state of the art plan we used compensated for motion and errors by adding large margins and this means the CTV/PTV surface ratio is pretty low. A lot of spots are then delivered outside the CTV to assure the target coverage. We can

see that the starting moment can have an effect on the fraction of spot weights passing through the CTV (7% difference between best and worst case for the sagittal plane). We still need to see how we could relate this kind of information to a dose distribution.

4.2.4 Conclusion and future work

This tool will allow us to simulate and observe different treatment strategies. In this first experiment, we simply observe a state of the art plan like the ones currently used in clinical practice. In the future we want to compare this plan to other treatment strategies that take advantage of the real-time imaging possibilities. Using deformable registration of the dynamic MRI sequences on the 4DCT, we hope to be able to recompute a variable range in real-time, synchronized with the MR images and later, recompute useful information about the real dose distribution. A complete Dose Volume Histogram (DVH) seems out of reach for now but a partial DVH inside a slice may be a good starting point towards a real time dose deposition information. This tool could also be used to study interplay effects [8] or to estimate the potential gain in margins of an hybrid MRI-Proton device and to evaluate the potential gain of designing such a machine and define the necessary constraints in imaging quality and speed for it to be really useful.

4.3 Towards Real-Time proton range verification using dynamic MRI

4.3.1 Context and objective

With the arrival of hybrid Photon-MRI solutions in standard radiotherapy [2], real-time adaptive treatment or treatment verification are on the way. In proton therapy, the hardware solution does not exist yet but is under serious consideration [70, 41]. Proton treatments, with their particular dose distribution profile, should benefit even more than photons of such an hybrid device. In this context, we developed a tool to study the possible new treatment strategies that could emerge from such an hybrid machine and their possible gain. This particular work aims at visualizing a proton PBS treatment plan on continuous 2D MR images.

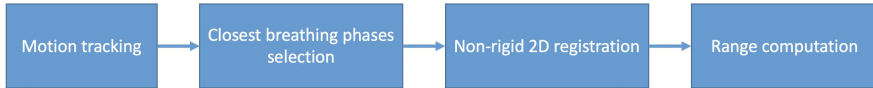


Figure 4.4: Pipeline of the method. After the motion is tracked, a CT slice that shows a rough approximation of the diaphragm position of the MRI slice is extracted from the closest phase in the 4DCT. Then, this CT slice is non-rigidly registered with the MRI slice to get a better matching image, on which the spot range is recomputed.

By tracking the motion of the diaphragm on the dynamic MRI image series, we create a CT image sequence that follows approximately the same breathing motion pattern. The proton spots range is then recomputed on the CT images and this recomputed range (RR) is compared with the planning range (PR) that was previously extracted from the treatment plan.

4.3.2 Materials and methods

The method pipeline is represented in Figure 4.4. First, the breathing motion is tracked on the MRI dynamic sequence using an in-house tool to track anatomical interfaces (cf. chapter 3). The MRI dynamic sequence is used as the ground truth showing the real anatomy and target position variation over time. For each new frame, the tracked motion amplitude is compared to the 4DCT motion to select the phase and slice which is the closest from the current MRI frame [Figure 4.5]. This gives a matched CT sequence which is a rough approximation of the MRI sequences. It already follows the irregular breathing pattern, which was not the case when only using the original looped 4DCT.

Then, a fast 2D non-rigid registration is computed to deform the selected matching CT slice on the current MRI frame, to imitate the irregular breathing motion seen on the MRI as best as possible [Figure 4.6]. This registration was done using the Elastix registration tool [49] with a mask for the bone structures over the CT images. We can see that both motion signals are closer after registration, but still not exactly the same. Errors can come from the motion tracking step or from

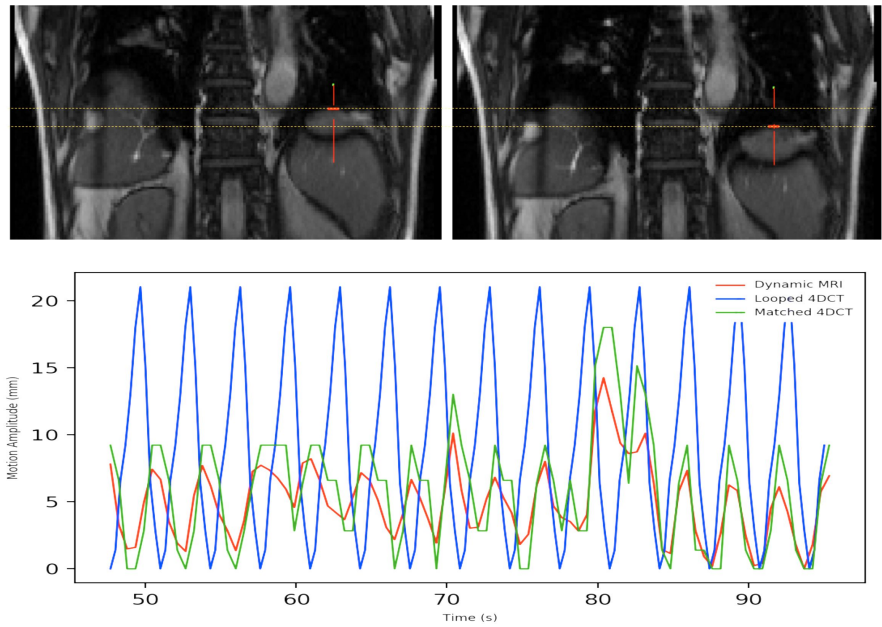


Figure 4.5: Two examples of diaphragm amplitude tracked through time on MRI and resulting motion signals for MRI, Matched CT and original CT

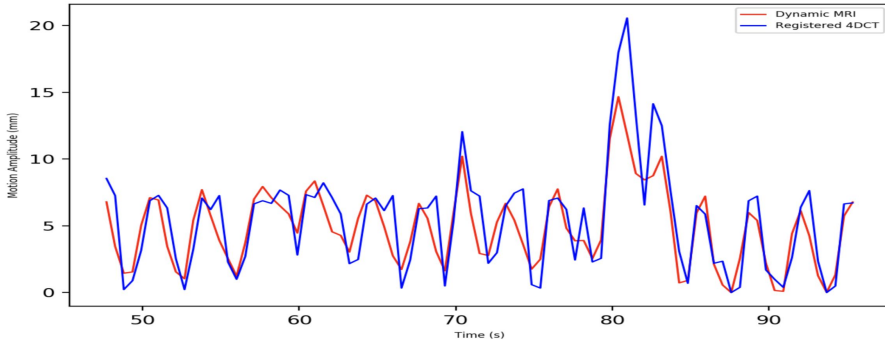


Figure 4.6: Comparison of motion amplitude observed on the MRI sequence (red) and on the registered CT slices (blue).

the spatial registration. We have not yet done an experiment to measure the quantity of errors coming from each source.

Finally, the spot range is recomputed on the deformed CT for the spots passing through the slice and delivered during the current frame acquisition time (around 400 ms for our first tests).

The image data, (MRI BSSFP sequences acquired on a Siemens Skyra 3 Tesla scanner, and the 4DCT) come from patients treated for primary (hepatocarcinoma) or secondary (metastasis) liver tumors by radiotherapy. A PBS proton plan was then computed on the Raystation⁶¹ to get the proton treatment plan information.

4.3.3 Results

The breathing motion measured on the deformed CT seems to be well matched to the dynamic MRI, with a mean difference under 2 mm between both signals. The matching/registration methods can still be improved to imitate better the real motion, specifically in case of irregular breathing patterns (in figures 4.5 and 4.6, the high peak around 80 sec is not well matched). The method runs in 2 seconds/frame on a 4 core laptop. As the MRI acquisition rate is 2.5 Hz, this is not performed

¹<https://www.raysearchlabs.com/raystation/>

in real-time yet but we think it could already be fast enough with more computation power.

The recomputed range after registration should, for the majority of the delivered spots, imitate better the reality than the range computed during the planification. Preliminary results shows that a large fraction of the recomputed spot range differ significantly from the planned range. For spots delivered through a sagittal plane, we measured differences from -9 to 54 mm (Mean = 20 mm, Std = 11 mm) and between -10 and 90 mm (Mean = 41 mm, Std = 26 mm) for the spots in a coronal plane. We only tested one plan and one patient so far, and with the target close to the diaphragm, a difference of several centimeters like we got is not really surprising. For 10 simulations, the average difference was not affected much by changing the delivery starting time.

4.3.4 Conclusion

This method and the associated tool allow a better estimation of the motion impact on proton spot range. The preliminary results have to be considered carefully. The quality measurement of the simulated motion is only based on the diaphragm and more motion comparisons still needs to be done (skin, ribs, ...). The tool will allow us to compare and evaluate the quality of different treatment strategies and also study different approaches to improve treatment plans by simulating the existence of an hybrid MRI- Protontherapy machine allowing simultaneous imaging and treatment.

Chapter 5

Continuous Real-time 3D Motion Reproduction Using Dynamic MRI and Precomputed 4DCT Deformation Fields

This chapter covers our method to drive a 3D motion model using dynamic 2D MRI slices. It results in a set of 3D images that follow the breathing pattern of the patient throughout the entire duration of the dynamic acquisition, mimicking irregularities or shifts in the breathing pattern. The first results of this work were presented at the International Conference on the Use of Computers in Radiation Therapy (ICCR) in Montreal in 2019 [21], and the complete version was published in the Journal of Applied Clinical Medical Physics in 2020 [25].

5.1 Introduction

The goal of radiation therapy is to irradiate tumors while preserving healthy tissues and organs at risk. The treatment plan is generally designed on X-ray 3DCT images to ensure conformity between the planned dose and its delivery. In the case of moving organs encompassing the

respiratory movements, such as liver and lungs tumors, the treatment has to integrate the respiratory motion in a consistent way, from planning to delivery. One way to take this motion into account is to estimate it by using a 4DCT and provide motion margins to ensure the target coverage [46, 88, 50, 105]. This lowers the risk of mistreating the target but also irradiates more healthy tissues, potentially creating complications [61]. Unfortunately, a 4DCT is composed of reconstructed images, based on a couple minutes of acquisitions sorted and resampled together into a sequence of 3D images. Therefore, it does not represent the real continuous motion but the average motion of one period computed over several breathing periods. Even if the 4DCT is acquired in the same position and with the same constraints as during the treatment, several studies have shown that during treatment, the motion induced by the breathing can differ significantly from the motion captured by the 4DCT in the treatment planning step [27], resulting in potential errors or sub-optimal treatment.

Different methods have been developed to address the motion-related issues and increase confidence in tumor localization. Gating based on an external surrogate can be used but relies on the basic assumption that the correlation between internal and external motion has been the same at planning and in the treatment room [7]. Greater accuracy can be achieved by tracking fiducials implanted in the tumor [68], but this last solution requires heavy and risky invasive pre-intervention. Other methods have been developed to reduce the impact of breathing-related motion during treatment such as abdominal compression [57], audio coaching [33] or mechanically-assisted ventilation [72, 75]. These options yield lower motion amplitude or a more regular breathing pattern that can result in a first reduction of the motion margins, or a better gating or tracking precision.

The ultimate reduction in the motion margins would entail adapting the treatment in real-time, based on precise tracking of the 3D anatomical structures' volumes. This would make it possible to transform a complex 4D treatment into a sequence of more precise 3D treatments synchronized with the anatomical motion. To achieve this, the real time positions of the target and of the surrounding organs must be known throughout treatment delivery.

With the recent developments of hybrid Linac-MRI solutions in stan-

dard photon based radiotherapy [54, 67, 29], continuous real time MR imaging during treatment is now possible and more research is focusing on online adaptive treatment [2, 86, 79] and tumor tracking [15]. In proton therapy, no hardware solution is as yet available, but is under serious consideration [71]. MRI is the ideal imaging modality for this application. It can give good soft tissue contrast and it is not irradiant, which is crucial for an unconstrained use during treatment. Unfortunately, MRI devices do not allow real-time full 3D acquisition for now and therefore only 2D slices can be acquired in real-time during treatment to follow the motion (this is usually called cine or dynamic MRI). Full 3D motion must then be derived From this limited amount of geometric information using motion models [64]. Different methods have been developed to use 2D slices efficiently to drive 3D patient-specific motion models built on vector fields coming from non-rigid deformation algorithms. The diaphragm position can be used as a navigator [30], a PCA-based similarity metric can be derived from the vector fields [95], [40], or more recently ROI have been used to drive a motion model [32]. All these options are used to transfer the 2D motion information from dynamic 2D MRI slices to complete 4D motion retrospectively. The treatment delivery quality can then be controlled between fractions and the accumulated dose for both the tumor and organs-at-risk can be computed, taking the patient's real breathing motion into account. However, these methods are not fast enough to be used in real-time. Tumor tracking is sometimes possible using cine MRI 2D slices [13], but even with MRI soft tissue contrast the target is not always visible inside soft tissue such as in the liver.

While MRI is the ideal solution for continuous imaging during treatment, tissue density related images such as CT's are still necessary for dosimetric quantification. Recent results have shown that for standard radiotherapy and proton therapy alike, MRI-only workflows can be precise enough to generate virtual 4DCT images derived from 4DMRI acquisitions. This method can replace 4DCT acquisition in the planning phase and be used for dose calculation and image guidance [51, 77].

Another important issue is controllability. To be accepted as a real-time treatment guiding tool, such a method has to give real-time feedback to allow a treatment to be controlled and stopped in real-time if necessary. To address these issues, we propose a method to transfer,

in real time and continuously, the breathing-induced anatomic motion tracked on 2D dynamic MRI to a virtual 4DCT sequence. Like the previously mentioned motion models, the proposed workflow is based on precomputed deformation fields, but the driving mechanism is a simple multi-modal MRI-CT interface tracking method. It is designed in such a way that is reliable and controllable through observation of the results in real-time, allowing the practitioner in the treatment room to take immediate actions if necessary. It is also scalable in precision and can benefit from any future improvement in fast MR imaging. The method could be used as a treatment verification or guiding tool and as part of a real-time dose accumulation observation method for photons or protons (see Discussion section).

5.2 Method

The initial step of our method relies on the acquisition or creation of a 4DCT (referenced as 4DCTo for original 4DCT) before treatment delivery. Prior to the real-time application, deformation fields between the 4DCTo phases are computed using the diffeomorphic morphons algorithm [43] from the open source platform OpenReggui¹. This algorithm computes 3D to 3D deformation fields that are consistent with the anatomy of the organs (diffeomorphism allows elimination of unrealistic artefacts in the deformation field) and can be summed and scaled easily while preserving rotations. Using the deformation from the morphons, we also compute the midposition (MidP) image [105] offline prior to the real-time application. Two deformation fields are saved for each phase N of the 4DCTo:

- The deformation field between the MidP phase and the phase N.
- The deformation field between the phase N and the phase N+1 (the last phase is registered on the first one to create a cycle).

The continuous motion is captured through 2D dynamic MRI sequences. The acquisition frequency of the dynamic MRI is chosen high enough to be able to follow the breathing motion of the patient, creating a 2D video of the breathing pattern (cf. section 5.2.6). The motion

¹<https://openreggui.org/>

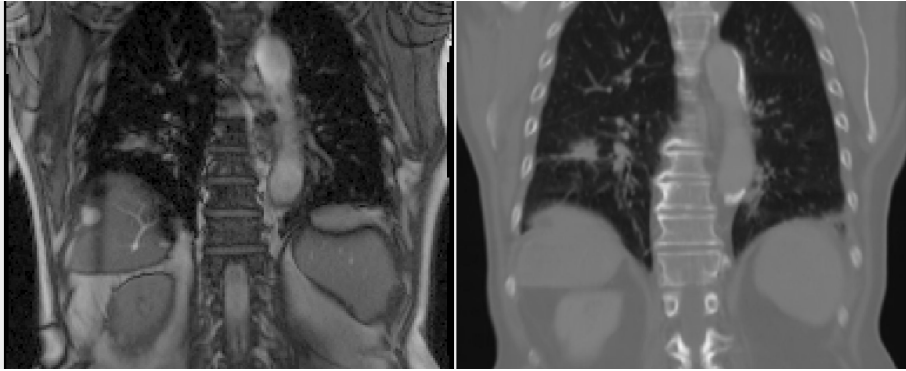


Figure 5.1: Example of 2DCT slice extraction after rigid registration of MRI on the 4DCTo

will be tracked on those image series using interfaces between moving anatomical structures.

While the 2D acquisition is running, the last step before launching the real-time tracking is to find the position of the dynamic MRI plane inside the 4DCTo. This way, the corresponding 2DCT slices are extracted from the 4DCTo to form a short 2DCT video of 10 frames in the same plane position as the 2D MRI [Figure 5.1]. This is done using the first few MRI frames of the sequence, based on the matching of non-moving bony structures such as vertebrae. This can be done using multi-modal rigid registration, but for the 15 patients in this study we did it manually. In a real treatment situation, it would be done right before the start of treatment.

The general workflow of our approach is summarized in Figure 5.2. Using the two data sets, namely the continuous 2D MRI and the 4DCTo with the associated deformation fields, our method transfers the positions of tracked anatomical structures from the 2D MRI frames to a new set of virtual 3DCT phases in real-time. A 3DCT image is generated for each MRI frame by inter- or extrapolating the deformation fields to constitute the continuous virtual 4DCT (4DCTc). Note that by using precomputed deformation fields to deform 3DCT images, our method relies on the hypothesis that breathing-unrelated anatomical changes such as stomach fullness, bowel gas, tumor growth/shrinkage and patient weight loss stay small between the 4D image set acquisition and

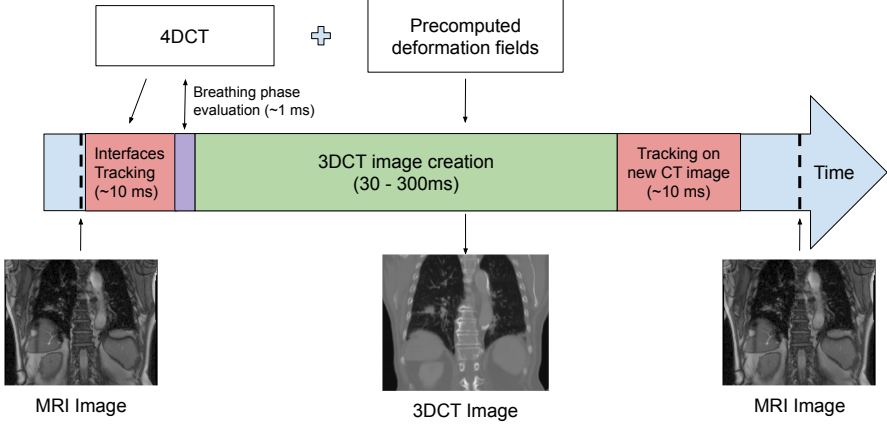


Figure 5.2: 3D real-time motion reproduction workflow

the application of our method, at least in the treatment path. Under this condition, the entire 3D motion description based on a small set of 2D slices is reliable. If it is not the case, the quality of our results might drop but the validation step which is also part of the real-time workflow will detect the difference and let the user to take action if necessary (cf. discussion section). The different steps in the process are detailed in the following sub-sections.

5.2.1 Interface tracking

The breathing-induced organ motion and positions are captured by tracking the interfaces between two tissues. To track an interface, the user can place a navigator, a small line in the direction of the motion and crossing the interface to track. The tracking works with a simple image processing pipeline [Figure 5.3], occurs in real-time (2ms per navigator) and is robust to noise. The name “navigator” is borrowed from the MRI navigator echoes, a 1D acquisition MRI scanners can acquire and use to sort images in post processing or trigger acquisitions [44, 96]. In this case, the 1D vector is a vector of pixels manually selected on the frame, but the outcome is similar. We chose to position them manually for reasons linked to reliability and controlability by the practitioner and are developed in the discussion section.

When an interface is chosen on one image series, a navigator pair is

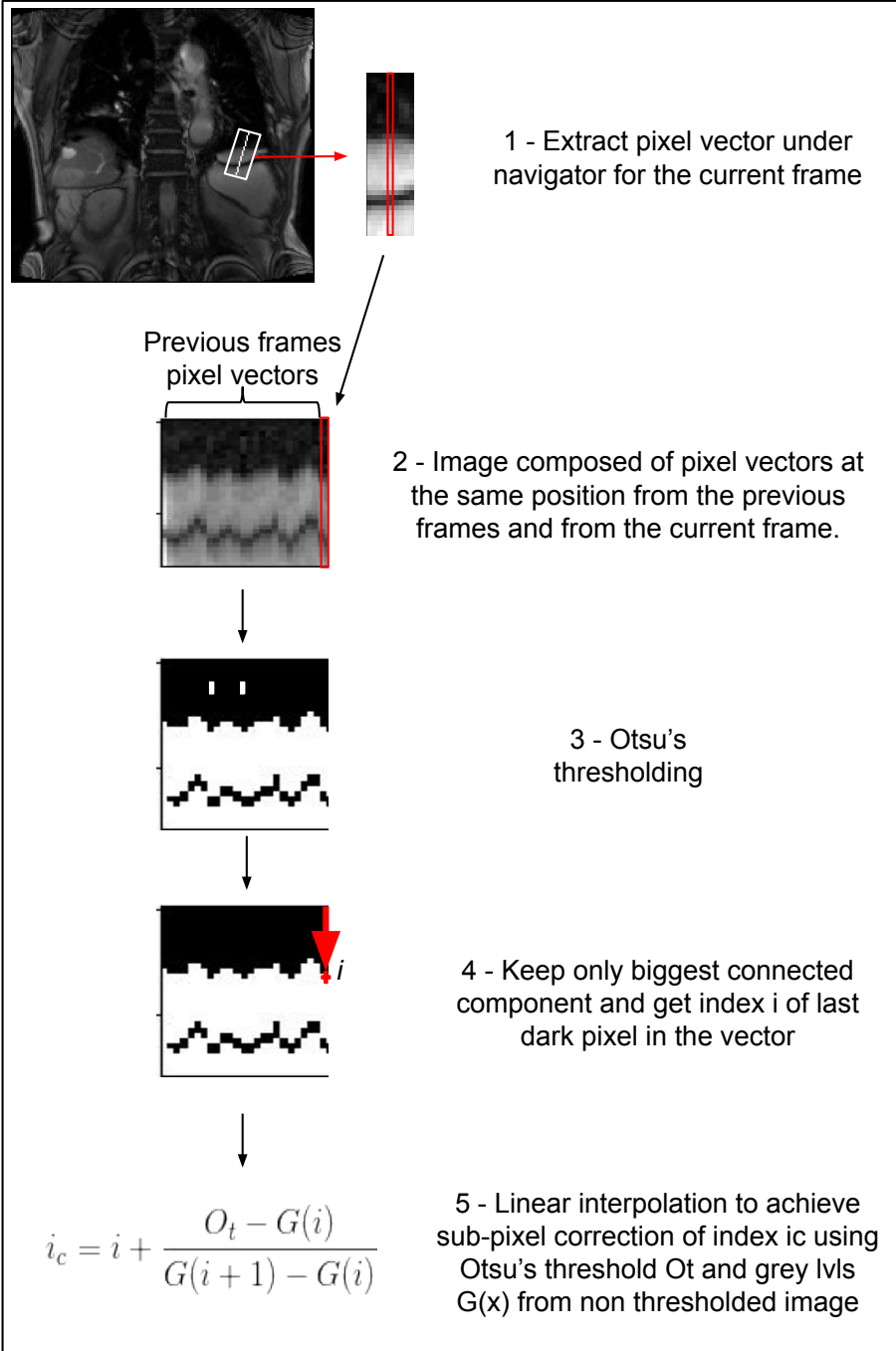


Figure 5.3: Steps of the interface tracking method.

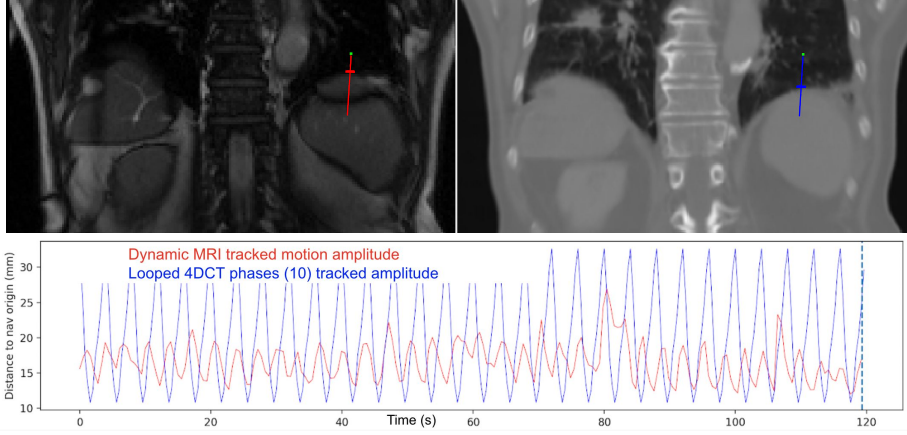


Figure 5.4: Example of motion amplitude tracked on both the 216 frames of the dynamic MRI (in red) and on the 10 looped frames of the 4DCTo (in blue). The tracked motion is given as the distance between the navigator end (green dot) and the tracked interface (small perpendicular line) in mm.

automatically created to track the same interface on both image series using the registration of the MRI position on the 4DCTo. The tracked position is given as the distance between the navigator end and the tracked interface in mm. The interface motion measured on the MRI frames is compared to the one measured on the 10 frames of the 2DCT video [Figure 5.4]. To verify that the tracking on the two different image modalities does not create an error caused by the difference in contrast and grey level representation of tissues, we performed a test on 25 pair of images made up of an image of each modality. On those images, a tissue border is visible and at the same position on both image modalities [Figure 5.5]. Then, 3 navigators are applied on each image pair to find the border position. By measuring the difference between the detected border positions inside a pair of navigator, it is then possible to evaluate the tracking difference caused by the contrast difference. For the 75 navigator pairs tested, the average distance between the detected border positions on the CT and on the MRI image was 0.21 mm (std 0.18 mm). This is a small difference but needs to be considered in the residual error margin.

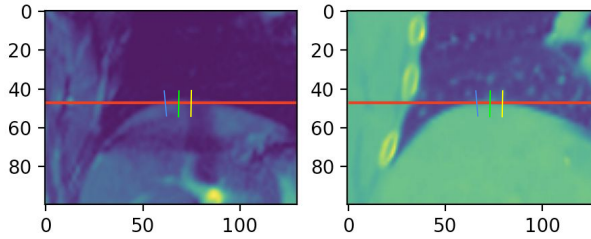


Figure 5.5: Example of image pair used for the evaluation of the tracking error resulting from image contrast differences. The MRI (left) and the CT (right) images are chosen by visual comparison such as the diaphragm position is at the same height (red horizontal line). Then, 3 navigators pairs (blue, green and yellow lines) are placed at the same position on both images to compare the respective detected position of the diaphragm in each navigator pair.

As the aim is to reproduce with fidelity the motion of the tumor, of surrounding tissues and of anatomical structures in the path of a photon or proton beam, these regions are our main concern and were chosen in priority on all the sequences to place the navigators. A set of 2 to 5 navigator pairs was used for each MRI slice position, depending on the quantity of interesting tissue interfaces that were visible on both the MRI and CT images. In most cases, tumor borders were not visible enough to be tracked on either the MRI or CT image series. We chose interfaces with which the tumor motion seemed highly correlated, but we did not compute the correlation coefficient for this work. As the navigator positions are chosen manually by observing the images, MRI and 4DCT visible imaging artifacts are avoided as well and supposed not to have impacts on the results [cf. section 5.4.3].

5.2.2 Phase selection method

Once the interface position is measured on the 10 phases of the 4DCTo and at the same position for the new MRI slice, both motion signals are combined to determine which phase has to be created with the following steps:

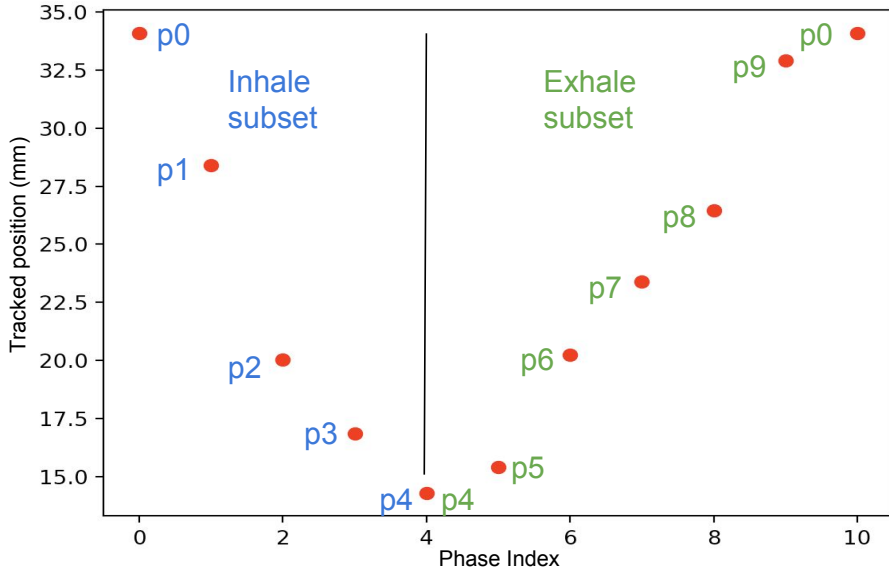


Figure 5.6: Separation of the 2 phase subsets. The tracked position on each phase, as well as their order, are used to split the 4DCT in two subsets. The increasing part forms a subset and the decreasing part the other subset.

1. Check the current breathing state Comparing the positions measured between the new MRI frame and the previous one determines the current breathing state as inhaling or exhaling. The state is then used to select the corresponding subset in the 4DCTo phases [Figure 5.6].
2. Find the closest phase in the breathing state subset of CT phases The breathing amplitude position measured on the MRI frame is compared with the amplitudes of the selected subset of CT phases to find the closest phase from the MRI amplitude.
3. Compute an inter- or extrapolation ratio by comparing the measured motions A ratio index is computed using the positions measured on the MRI frame and on the closest CT phase found in Point 2 [Figure 5.7]. Two cases must be considered:
 - Interpolation: The MRI position F_p is inside the range of the

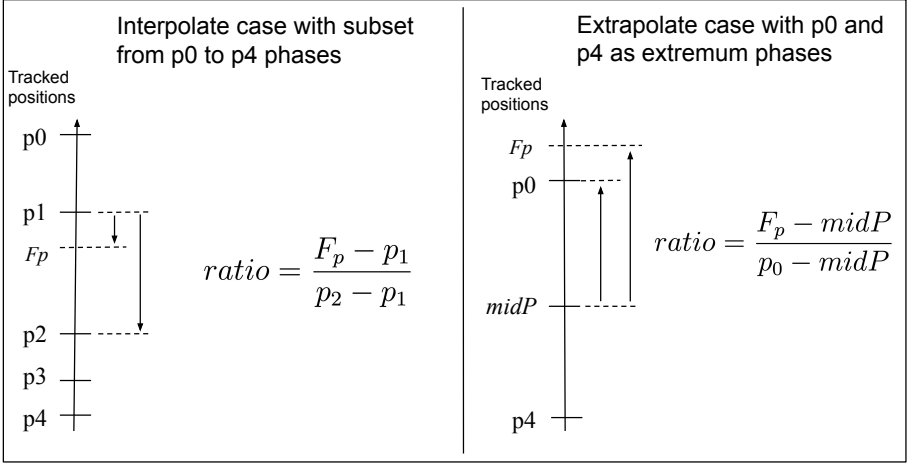


Figure 5.7: Example of phase ratio computation in the case of interpolation (left) and extrapolation (right). F_p is the new frame position and midP is the mean position of all the phases (not just the subset).

CT phases amplitude

- Extrapolation: The MRI position F_p is outside the range of the CT phases amplitude

For the extrapolation case, we decided to use the MidP phase to compute the ratio to avoid bending the motion trajectory away from the main motion direction in the case of hysteresis motion as represented in Figure 5.8.

5.2.3 Multi-navigator average phase selection

To reduce image noise impact on the phase selection method, the resulting phase estimations coming from the n navigators are combined to compute an average of the resulting phases [Figure 5.9]. First, the phases p_n are transformed into angles θ_n between 0 and 2 using the number of phases N in the 4DCTo [Eq. 1], such that the phases become periodic and phase 0 follows phase 9. In this set of angles, if a phase given by a navigator is too far from the others, it is considered an outlier and removed. Then, the remaining angles are used to compute a new

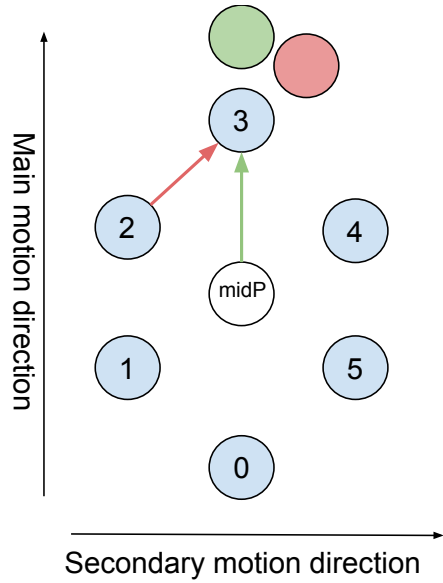


Figure 5.8: Example of hysteresis trajectory of an object in 2D. Positions in the 4DCTo phases are represented in blue. Results of extrapolation of the deformation fields are shown using the midP phase (green) or the N-1 phase (red). The motion in the second direction is highly exaggerated for illustration purposes but shows the difference that the two approaches can create.

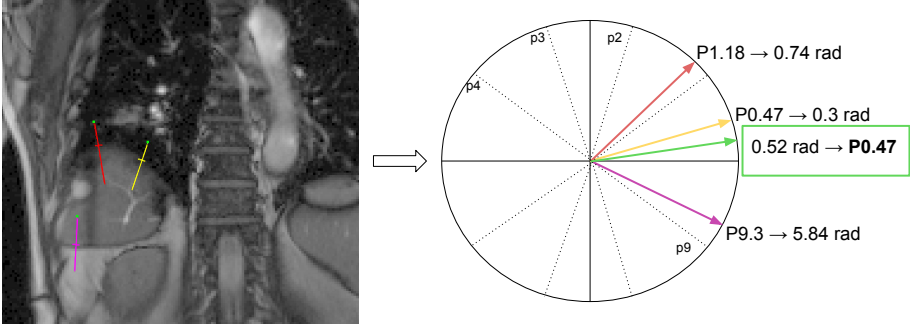


Figure 5.9: Example of average vector and resulting phase (in green). The red, yellow and purple navigators phases are transformed into their respective angles, then used to compute an average angle and transformed back into the corresponding phase.

angle θ_f corresponding to the average of sines and cosines of angles θ_n [Eq. 2]. Finally, the angle θ_f is transformed back into the final phase value p_f [Eq. 3].

$$\theta_n = \frac{2\pi p_n}{N} \quad (5.1)$$

$$\theta_f \equiv \begin{cases} \cos \theta_f = \frac{1}{n} \sum_n \cos \theta_n \\ \sin \theta_f = \frac{1}{n} \sum_n \sin \theta_n \end{cases} \quad (5.2)$$

$$p_f = \frac{N\theta_f}{2\pi} \quad (5.3)$$

5.2.4 3DCT phase creation

The final step is to generate the new 3DCT phase. The velocity field between two phases, N and $N+1$ in interpolation cases or MidP and N in extrapolation cases, is multiplied by the interpolation or extrapolation ratio. Then, in order to use it to deform an image, the velocity field has to be converted into a deformation field using field exponentiation. Finally, the phase N is deformed using this interpolated or extrapolated deformation field to generate a new 3D phase matching the MRI motion amplitude.

We ran this method on a decent laptop. Creating the entire 3DCT image for each MRI frame took around 2 seconds by frame. It is too much to be used in real time, since we only have from 220 ms to 320 ms between 2 frames (See Materials). However, limiting the region to deform to the areas around the navigators and the treatment path greatly reduces the time required to create the image. To determine this area of interest, we used the treatment plan to get the treatment path, on which we added 2 cm on every side before cropping the image. The creation of such a partial image took only between 30 and 300 ms. This can still be improved by using dedicated hardware (cf. Discussions section). Full images were also created anyway (not in real-time), for the sake of simplicity for displaying and observing the results.

5.2.5 Validation

The evaluation of the quality of the results is also part of the real-time process. To see if the motion of the MRI is well matched, pairs of navigators are applied again, this time on the current MRI frame and on the 3DCT we have created for this frame. As the MRI contains the ground truth anatomy that we aim to replicate with the 4DCTc, this difference should be as small as possible. This comparison is done for two navigator sets:

- Used navigators set (UN): Navigator positions that were used previously and from which the new image has resulted.
- New navigators set (NN): Navigator positions that were not used previously to create the new image.

The absolute value of the difference between the two positions is computed for every new frame and all navigator pairs. At the end of the sequence, the average of this difference along the entire 4DCTc is computed.

The difference is measured for multiple navigators, but all in the same slice. That means that the farther we go from the MRI slice position, the less likely our deformed image is to match the patient's real anatomy exactly, because the distance to the ground truth increases. If the tracking difference is low even for navigators of the NN set placed far

away from the rest of navigators (more than 20 cm away, for example), it shows that there was not a lot of non breathing-related changes between the two images and that our hypothesis is verified. It is a good indication that the deformation in the third dimension should also behave well. Due to the nature of our method, we think using the NN set is enough to validate the method, and that a full 3D validation will not provide useful additional information on the correct functioning of the method. Indeed, even if a navigator can be placed anywhere on the image with any direction, it still uses only localized 1D information. Then, one or more of these 1D information is used to drive a 3D deformation. As long as the new region, selected for the validation, is not the same as one of those used for the driving of the motion model, it does not matter if this validation region is also in the slice or not [Figure 5.10]. There is no particular link created by our method between an area used for the deformation and an area that is not used but in the same slice. That is why we did not do a validation using a 3D image set as the source of the dynamic 2D image sequence. Now if a larger difference is measured between the tracking of a navigator pair, it signals that either that non breathing-related anatomical changes occurred or that the breathing pattern deviates greatly from what is contained in the 4DCTo (a big extrapolated case, for example).

The important part of the image is the beam path and we think a small set of 2D slices is enough to capture with precision what happens in this area, with the possibility of linking the treatment to the acquisition so as always to acquire images where the beam is currently irradiating.

Interleaved planes such as we have, or multiple slices in the same plane, while not technically a 3D validation, are used to validate the quality of the transferred motion for different planes successively, several times each second.

5.2.6 Material

Patient data come from 15 patients treated for primary (hepatocarcinoma) or secondary (metastasis) liver tumors by radiotherapy. For their treatment, a 4DCT was acquired in the treatment position, with abdominal compression and audio-coaching to regularize the breathing pattern. We also have treatment plans for these patients. We did not use them to compute doses but simply to get the treatment path (See 3DCT phase

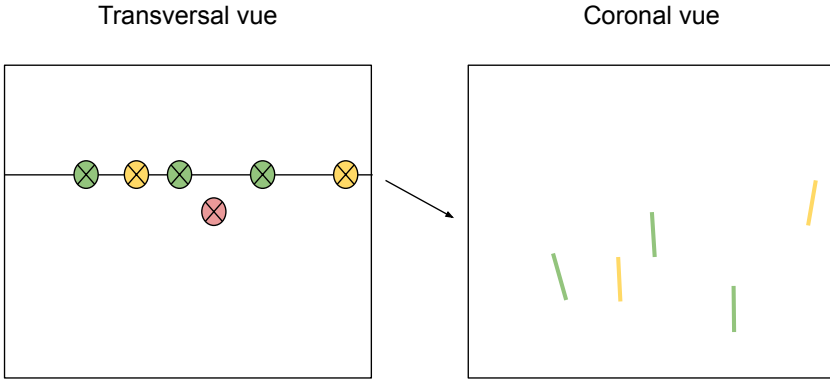


Figure 5.10: Example of new navigator selection for the validation. If the 3 green navigators are used to find how the image must be deformed, the two yellow one can be chosen to validate the resulting image. As only 1D localized information is used for each navigator, independently from one another, using the navigators in yellow or using the red position showed on the transversal view outside the coronal slice is similar. For this reason and because we do not have a 3D ground truth data accessible, we chose not to use a 3D image to validate the method.

creation). This trial was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, approved by our local ethics committee (B403201628906). Informed consent was obtained from all participants before the trial.

The MRI sequences were True FISP sequences from a Siemens Skyra 3T scanner. These were acquired the same day and under the same conditions as the 4DCT, with abdominal compression and audio-coaching. We acquired one to four different sequences on each patient using different numbers of slice positions, slice orientations, and acquisition frequencies. Some of the sequences were acquired several times, depending on the patient's comfort during the MRI or the available scanner time. The acquisition frequency was set to between 1.5 Hz and 3.16 Hz so that we could follow the breathing motion while keeping pixel size under 3 mm for image quality (see discussion). The different slice position choices and acquisition parameters are described below. .

1. Single slice in sagittal or coronal plane (14 sequences for 14 positions) - 3.16 Hz for 380 slices in 2 minutes - TE: 1.41, TR: 3.23, 208x204 pixels of 1.6x1.6x7 mm
2. 2 interleaved coronal and sagittal slices (12 sequences for 24 positions) - 1.83 Hz for both orientation (3.66 Hz in total), 440 slices (2 x 220) in 2 minutes - TE: 1.39, TR: 3.16, 188x192 pixels of 1.82x1.82x7 mm
3. 3 contiguous slices in sagittal or coronal plane (12 sequences for 36 positions) - 1.5 Hz for the 3 slices (4.5 Hz in total), 540 slices (3 x 180) in 2 minutes - TE: 1.33, TR: 3.01, 126x128 pixels of 2.5x2.5x7 mm

In total, 74 different 2D slice positions acquired for 2 minutes were available to track the breathing motion for a total of more than 17000 images. Every position was used independently, meaning that when the two interleaved coronal and sagittal slices were used, each frame of each orientation was used to track the motion and to create a 3DCT image.

5.3 Results

For partial images limited to the navigators and the beam path areas, it takes 2 ms per navigator to track borders positions, between 30 and 300 ms to create the new deformed image and 2 ms per navigator to track the borders again on the new image to evaluate its quality. The complete process takes between 40 and 320 ms depending on the number of navigators and the size of the area to deform.

When measured on the navigators of the UN set, the absolute value of the motion signals difference between the MRI and the 4DCTc was usually under 2 mm in average during the 2 minutes of acquisition (Example in Figure 5.11). The average and maximum difference for all patients are reported in [Table 5.1]. The same results for the NN navigator set are reported in [Table 5.2] and the difference between the MRI and the 4DCTc motion was for most sequences higher than in the UN cases. We observed that even if the frequency of the motion was well matched, the amplitude of the MRI was not always reproduced correctly and a shift between both motion signals could appear [Figure 5.12], especially for navigators of the NN set if placed far from the UN ones. Note that the max difference corresponds to the worst case of all our images and for all our navigators (more than 17000 images with several tracked positions on every image).

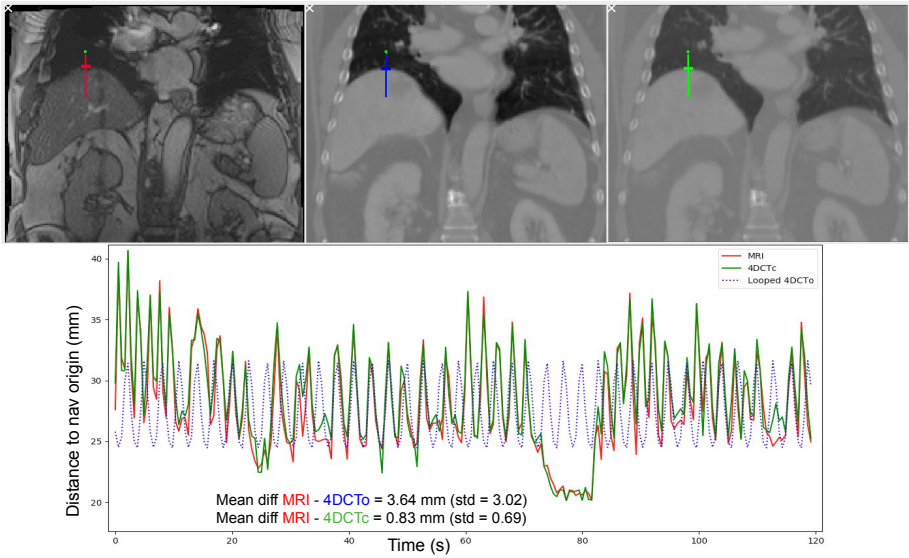


Figure 5.11: Example of motion comparison between the MRI sequence, the created 4DCTc and the looped 4DCTo and the resulting mean difference between motion signals.

UN cases	Mean diff 4DCTc	Max diff 4DCTc	Mean diff 4DCTo	Max diff 4DCTo
1.6 mm (14 positions)	1.75 mm (std=0.76)	12.06 mm	9.4 mm (std=6.2)	33 mm
1.82 mm (24 positions)	1.64 mm (std=0.9)	11.34 mm	8.94 mm (std=7.1)	37 mm
2.5 mm (36 positions)	2.03 mm (std=1.4)	12.22 mm	7.34 mm (std=2.23)	29 mm

Table 5.1: Results for motion measured at the phase selection positions (UN) for all patients, separated by pixel spacing (1.6, 1.82, or 2.5 mm).

NN cases	Mean diff 4DCTc	Max diff 4DCTc	Mean diff 4DCTo	Max diff 4DCTo
1.6 mm (14 positions)	2.48 mm (std=0.6)	9.58 mm	9.14 mm (std=5.45)	24 mm
1.82 mm (24 positions)	2.2 mm (std=1.18)	19.57 mm	6.08 mm (std=2.52)	32.92 mm
2.5 mm (36 positions)	3.92 mm (std=2.22)	11.3 mm	7.97 mm (std=2.77)	31 mm

Table 5.2: Results for motion measured at other positions (NN) for all patients, separated by pixel spacing (1.6, 1.82, or 2.5 mm).

The same results are reported in Table 1 and 2 for the difference between the MRI and the 4DCTo where the looped 4DCTo was synchronized with the audio coaching loop. It is reported as a comparative element and shows the gain of copying the motion using our method vs simply using the 4DCTo.

The MRI motion was usually well reproduced by the 4DCTc, even with irregular breathing patterns [Figure 5.11]. However, our method's precision started to drop in extreme cases of motion extrapolation, where the MRI tracked point was really far out of the 4DCTo range. This is caused by the fact that extrapolation also multiplies the errors by the extrapolation phase ratio. In some extreme cases, it can create a big difference between the MRI frame amplitude and the reconstructed 4DCTc phase [Figure 5.13]. Of all the 74 MRI positions used, the worst results shown in [Table 5.1] and [Table 5.2] by the maximum difference column were all results coming from extrapolation cases with high extrapolation ratios.

The image resolution did not seem to have an important impact on the motion tracking and reproduction quality. But to be as close as possible to the real anatomy of the day, we would recommend a resolution as high as possible to represent the tracked interfaces' positions more precisely and ensure a higher quality 4DCTc.

5.4 Discussion

5.4.1 4DCT reliability and inter-fraction

As mentioned in the method section, we suppose that inter-fraction variations such as tumor baseline shift, tumor shrinking and stomach/bladder filling will be checked prior to delivering the daily fraction, using online pre-treatment MRI imaging, for example. Parts of the anatomy in the 4DCTo can be deformed or shifted compared with continuous MRI and the slightly worse outcome of our measurements in NN cases compared with UN cases confirms that our hypothesis was not always verified everywhere in the anatomy. The validation step applied as part of the real-time workflow is there to verify the hypothesis during the entire application and can be used to raise a flag and stop the treatment if necessary.

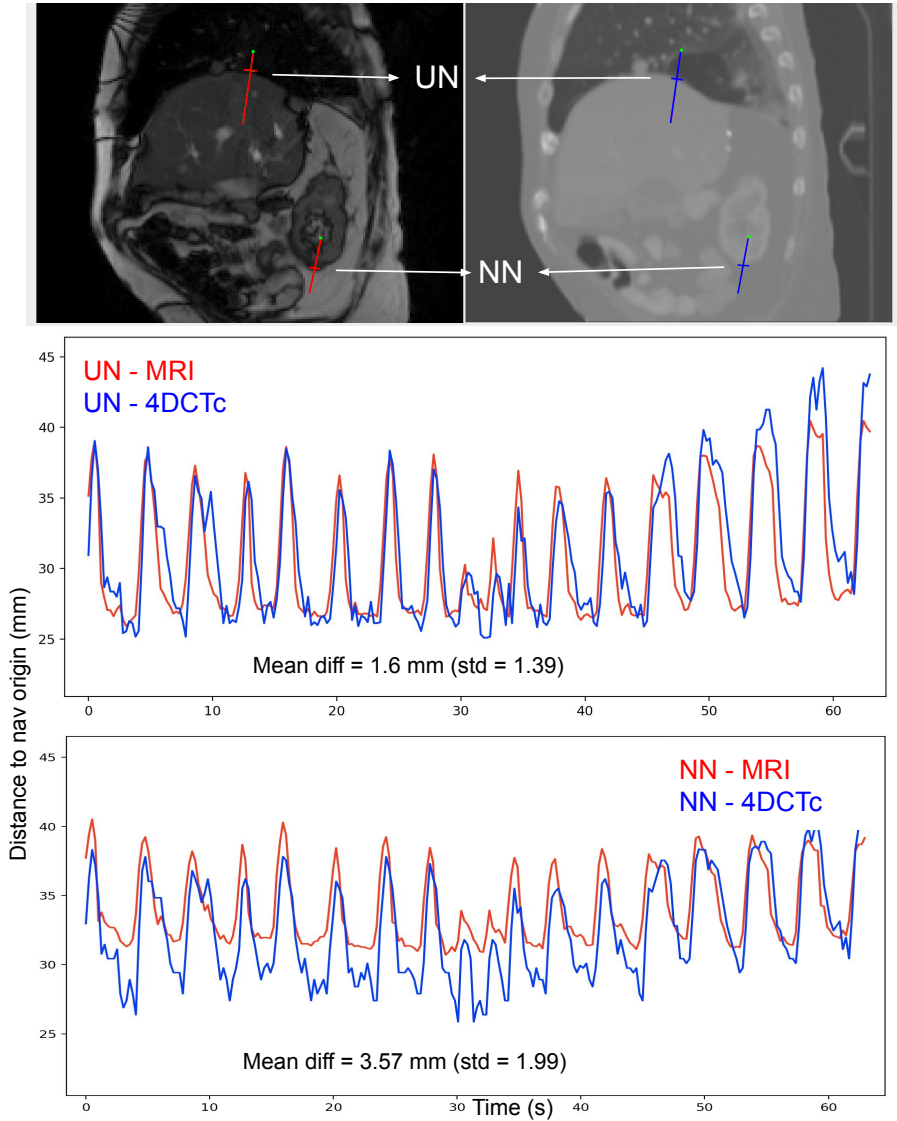


Figure 5.12: Example of motion comparison between MRI (left image) and 4DCTc (right image) in UN (top) and NN (bottom) cases.

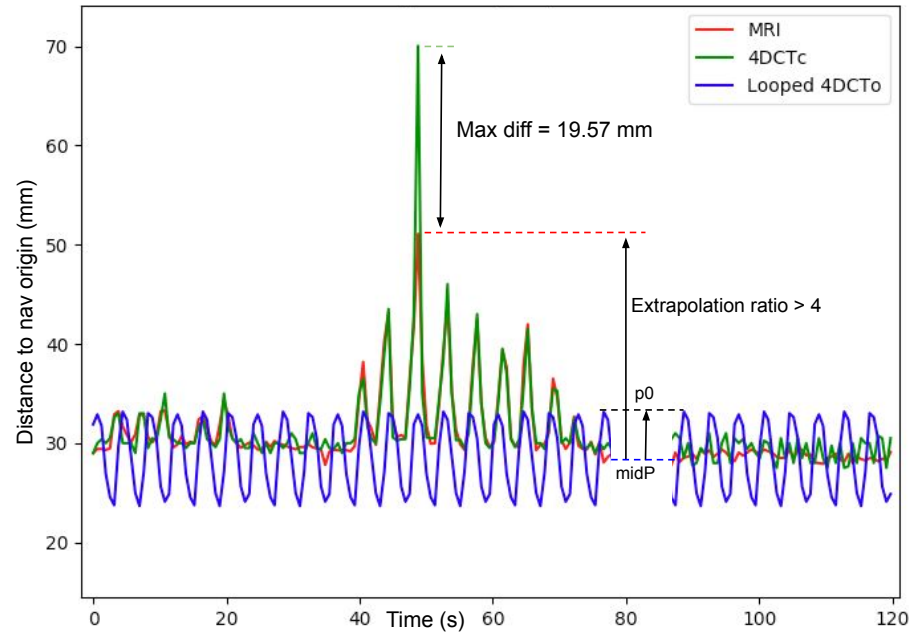


Figure 5.13: Example of extreme extrapolation case multiplying small errors.

Generally speaking, the more recent the image the more reliable it is. For this reason, updating the 4DCTo and corresponding deformation fields right before every fraction would be ideal. Options are being developed using, for example, only one 3DCT image and a 4DMRI [14]. This way, it might be possible to generate a new 4DCT several times over the treatment period, each time an irregular change happens, without increasing the imaging dose given to the patient too much. This could be a complement to the setup phase of today's practice, in which images are already acquired to position the patient. If done in the treatment room, such daily acquisition would probably increase the length and cost of the treatment session, but if the motion margins can be removed with a new improved guided treatment, it might be worth it.

As our next step, we are working on a way to apply this method even in the case of inter-fraction changes between the anatomy of the day and the 4DCTo. In any event, it is important to focus on motion in the beam's path to create the 4DCTc to get the best results for a treatment verification/guiding tool.

5.4.2 MRI-CT spatial registration error effects on the motion model

As with every application using registration in medical imaging, an error in the registration step will result in an error further down in the application pipeline. In our case, an error in the manual registration can be of two types. The first one would be to have selected a wrong CT slice in the direction perpendicular to the MRI plane. As the MRI slices are thicker than the CT slices, multiple CT slices are added around the selected one and used to create an average slice for the tracking method (cf. section 3.3). In this case represented in Figure 5.14, the average image that is created using the CT slices is only partially superimposed with the MRI frame. If the organ border is inclined in the direction perpendicular to the slice, it will be represented shifted within the two frames, and results in a shift in the tracked position [Figure 5.15]. If n is the registration error as the number of slices between the correct slice and the manually selected one and T_{CT} is the thickness of one CT slice, the part of the thickness of the selected ct images that is outside the thickness of the MRI slice is in the worst case nT_{CT} . Using θ as the average angle to describe the tissue border steepness in this area, the

tracking error E_t caused by the registration error can be written as:

$$E_t = nT_{CT} \tan \theta \quad (5.4)$$

To prevent this error to have a substantial impact, choosing the borders to track carefully is important to avoid steep border in the direction perpendicular to the slices.

The second error type would be an error in one of the two direction followed by the image, during the step of point pairs selection used for the registration (cf. section 3.3). In this case, the evaluation of the induced tracking error is more direct. It is simply the distance between the selected point and the real position of the chosen structure. These two registration error types would need to be quantified by inter- and intra-user studies for the method to be used in clinical practice. They must be considered to define the final security margins of the treatment.

5.4.3 Manual tracker positioning

We chose to use a manual tracker positioning for different reasons. First, it lets one select an interface visible on both MRI and CT modalities, which is necessary for our method. Then, it allows to avoid MRI artifacts (balanced steady-state banding artifacts [38]) and 4DCT reconstruction artifacts. Finally, it allows the operator to select a moving interface in the path of the treatment and with which the target's motion is correlated. That is important because in the liver, the target is not often visible on images and it may not be possible to use the target as a tracking interface. The choice of correlated motion is important and must be done carefully, because 20% of liver tumors have been shown to follow a hysteresis trajectory and the liver can deform non-rigidly during the breathing cycle [48]. If the target is clearly visible on the MR images, it is usually not difficult to either find a correlated motion or at least check if the target's motion deviates too much from the motion used to create the CT images.

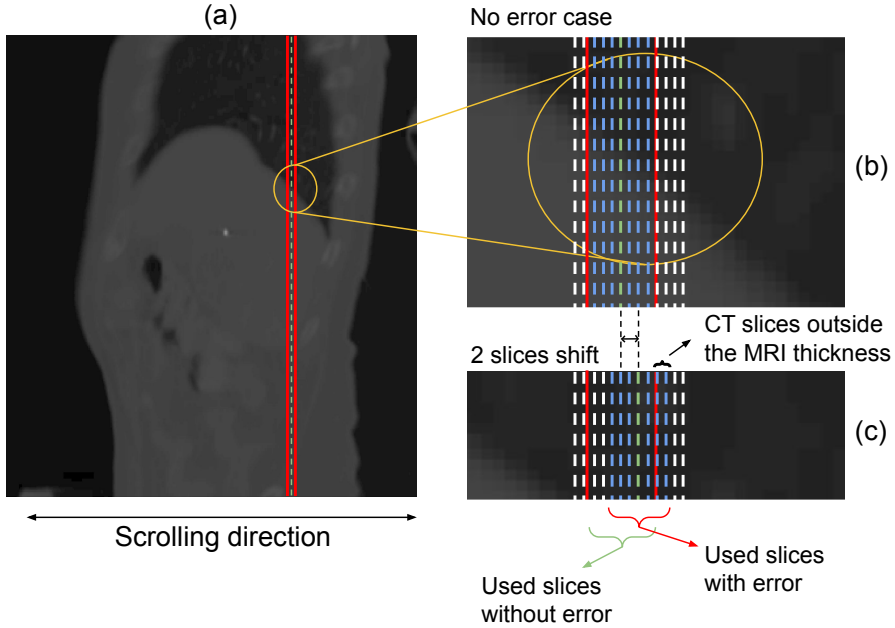


Figure 5.14: Example of error in the spatial registration resulting in an error in the selected CT slices. On a sagittal CT image is shown the coronal MRI plane thickness with 2 red lines, as well as the position of the coronal CT slice chosen by the manual registration with the green dashed line in between (a). On the right is shown first a case with no registration error (b), where the chosen CT slice (green dashed line) is in the center of the MRI thickness. In this case, 100% of the additional CT slices in blue are inside the MRI thickness. Then, a case with an error of 2 CT slices in the registration, creating a shift in the selected slices resulting in a fraction of the CT thickness outside the MRI thickness.

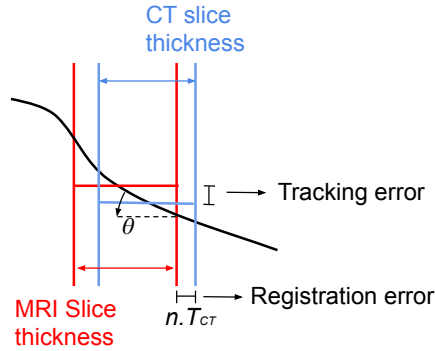


Figure 5.15: Example of interface tracking shift caused by a registration error. The black line shows the real position of the tissue border. The vertical red and blue lines the respective slice thickness for the MRI and the average CT slices. And the horizontal red and blue line the position of the interface detected by the tracker in both cases. We can see that if the organ border is inclined in the direction perpendicular to the slice, a shift between the two slices results in a shift in the detected border position. This shift is proportional to the registration error, in other words the number of error slices n multiplied by their thickness T_{CT} and to the steepness of the tissue border in this area.

5.4.4 Image acquisition frequency vs resolution and real-time use

In MRI, there is always a trade-off between acquisition frequency and image resolution. For this application, the priority was to follow the breathing motion in real time, including irregularities such as coughing or swallowing. For this, we recommend having at least 10 images by breathing period. Some patients can have a really fast breathing pattern, with a period under 3 seconds. In these cases, the image resolution and resulting precision of the tracking could be affected.

In the case of a fast breathing pattern, it might also be necessary to predict the motion to account for the image acquisition and image processing time. Motion amplitude prediction using the previous frames and the expected breathing parameters such as period and amplitude could be used to anticipate better which 3DCT to use. Note that this is not ideal because the point of a real time tracking is not to depend on predictions. If such a predictor is necessary, each prediction would need to be validated using the following frame to avoid accumulating errors.

We did not mention the latency between the moment a motion occurs and the moment it appears in the MR images due to the imaging time, image reconstruction time, and data transfers. It must be considered to implement a clinical real-time application. In the best case, it has been reported to be around 150 ms [12] for fast acquisitions on an MR-Linac. With MR-Linacs now available and online treatment guidance in development, we can hope for improvements in image acquisition and reconstruction speed, as well as in data transfer time.

Also, between MR slices, navigator echoes could be used to improve the temporal resolution of the tracking, as long as they can be positioned on an interface visible on the navigator echo specific acquisition and CT images. Studies have shown that it can be used to track interfaces on top of dynamic MRI images [94]. They have the advantage of being fast to acquire and process.

For a real-time use, several applications have to be considered:

- In order to be used as an offline tool to recompute the fraction dose afterwards, only the MRI acquisition needs to be fast to capture any irregularities in the breathing pattern. The method presented here can be used offline.

- Using this tool as a real-time anatomy-based guiding tool with pre-planned treatment means that tissue interface tracking and breathing state evaluation have to be done in real time, but these steps take only a few milliseconds. The main issue is the MRI acquisition and reconstruction time. This would really allow to gain in treatment precision, reduce or remove the motion margins and reduce the volume of healthy tissue hit. For the patients in our data set, we computed the PTV with and without the motion margins and observed a volume reduction without the margins up to 47% (Average = 28%, std = 17%).
- To be used as a real-time dose-based verification or guiding tool and to stop of the treatment if some criterion about the given dose is reached, the dose must be computed continuously and accumulated before any error in dose delivery becomes too great. In this case, the 3DCT image has to be created using deformation as part of the real time application. On this deformed image, the dose delivered during the current image timeframe must be computed as fast as possible to be able to raise a flag if necessary, before too much dose is given to healthy tissues. Such a fast dose computation method is difficult to achieve, but fast methods already exists [35, 63] and may become even faster in the future.

5.5 Conclusion

The proposed method can generate in real time a set of 3DCT images that imitates well the motion observed on dynamic MRI. Our method relies on a simple real-time interface tracking method and on precomputed 3D deformation fields. It could be used to recompute the delivered dose between treatment fractions more precisely, and eventually trigger a plan adaptation. It could also be used to compute the delivered dose in real time, either as a real-time verification tool or in the future as a real-time guiding tool for an on-the-fly adapted treatment method. Positioning the trackers manually requires a human intervention, but it also makes the method more robust to imaging artifacts or noise and gives the physician final control. The resulting 4DCTc quality is verified in real-time using the same tracking tool. Our next step will be

to use it to compare different treatment strategies to reduce the motion margins. The different treatment strategies outcomes can be compared by recomputing the delivered dose on the 4DCTc with consideration of the real motion tracked on the MRI sequences.

Chapter 6

Locally tuned deformation fields for 2D cine-MRI-based driving of 3D motion models

This chapter cover an additional step that can be added to motion models that are based on 4D imaging and precomputed deformation fields. It combines multiple breathing states using a weighted sum of multiple deformation fields. The resulting field is a better approximation of the ground truth motion. The first results of this work were presented at the Belgian Hospital Physicists Association symposium in La Louvière in 2020, and the complete version was submitted for publication in 2020.

6.1 Introduction

Targeting abdominal or lung tumors with radio- or proton therapy is not an easy task. The respiratory motion that occurs during the treatment, as well as more irregular motions such as bladder filling or systematic shifts in the patient anatomy have to be considered during treatment planing to be as accurate and robust as possible. Methods exists to mitigate the motion amplitude [57] or regularize the breathing pattern [75]. Margins are commonly used to ensure target coverage [50], and

sometimes robust optimization [16].

In recent years, MRI and radiotherapy have been combined in hybrid machines capable of delivering photon treatments and taking MR images simultaneously [19]. MRI presents better soft tissue contrast than CT scans with the added advantage that no imaging dose is given to the patient. For now, MRI is not fast enough to acquire time-resolved 3D images at sufficient frequency to follow the breathing pattern of a patient continuously; only 2D acquisitions are available at those frequencies. Research is currently aimed at driving a 3D patient specific motion model using 2D cine-MRI to reproduce the breathing pattern of a patient in 4D continuously for an entire treatment fraction.

Among the different methods that have been developed to achieve this [78], some use combination, interpolation or extrapolation of pre-computed deformation fields based on planning 4DMRI or 4DCT images, then apply the resulting field to a reference image to create the 3D anatomy of a specific time point. A PCA-based motion model can be used [95, 40] in which a global metric is computed using the entire slice or navigators extracted from the 2D slice [30], the motion happening out of plane can be quantified using a-priori information on planning data [92], as well as fast border tracking [25] (Our method presented in chapter 5) which uses an averaging over several local information and aims at being used in real-time. For these methods, the deformation of the reference image to get the 3D image to match the current 2D frame is applied globally without local adjustments using local information. The issue is that if non-breathing related motion happens between the acquisition of the motion model data and the treatment, the motion model might not contain the deformation necessary to reproduce the patient's current anatomy. To reduce this issue, methods using local information exists. An ROI-based model [32] has been derived from [30] and used to split the deformation fields into regions for each ROI. It improves the precision of the reproduced motion but takes too much time to be used online.

We propose a fast alternative way to tune global methods using local information. It allows to create images that are locally adjusted by combining several deformation fields, each created specifically for a certain area of the image. These areas can be chosen, to improve the quality of the model driving in the path of the beam and around the

target for example. We applied it on the border tracking-based method of chapter 5 [25] to implement this local tuning because it focuses on speed and online use. It could also be applied on other 3D motion model methods as long as the metric used by the model to match the 2D and 3D image can be computed piece-wise to different image areas. The resulting fields for each area can then be combined using our proposed fields combination.

6.2 Materials and Method

6.2.1 Preparation

Prior to the continuous application, a planning 4DCT (4DCTp) is acquired. From this 4DCTp, non rigid registration Morphons' algorithm [43] is used to get the mid-Position image (midP) [105] and the N 3D deformation fields $D_n(x, y, z)$ from the midP image to each of the N 4DCTp phases (Usually N=10). The advantage of this algorithm is that it gives velocity fields that can be summed and scaled easily, a property we will use for our method. This set of 3D images and 3D deformation fields is stored and forms the motion model.

Once the MRI sequence is launched, but before starting the generation of the continuous 4DCT (4DCTc), the MRI 2D plane positions have to be registered on the 4DCTp. For this work it was done manually using vertebrae since we have a limited number of patients, but it could be automated. This way, the CT slices corresponding to the MRI plane positions can be extracted from the 4DCTp to form a small 2DCT image series of N frames showing the same region as the MRI. Then, a small set of three to five interfaces is tracked using manually placed robust-to-noise border trackers as in chapter 5. The chosen interfaces must be visible on both MR and CT images, perpendicular to their motion and preferably with a large motion range. This can include hepatic dome, left diaphragmatic dome, visceral liver surface, kidneys, skin, ... The same regions are tracked automatically on both the 2D MRI sequence and the extracted 2DCT image series thanks to the registration [Figure 6.1].

The first 10 seconds of dynamic MRI frames are then used to compute an average tracked position $P_k = (x_k, y_k, z_k)$ for each of the K

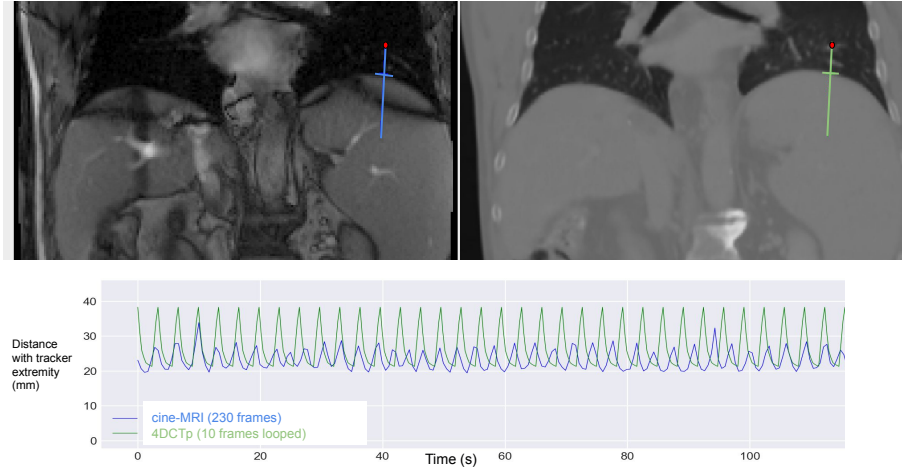


Figure 6.1: Example of tracker placed on the left diaphragmatic dome. The resulting motion signals are given as the distance between the tracker extremity (red dot) and the tracked border (small perpendicular line).

trackers T_k . This set of K 3D positions contain the positions on which the field will be locally adjusted. It is used to compute K 3D piecewise linear weight maps $W_k(x, y, z)$ according to the following steps, represented in Figure 6.2.

1. Create an empty matrix of the size of the 3D images.
2. Put the voxel at the position P_k to 1 and all other positions $P_{j \neq k}$ to 0.
3. Add points at the 8 corners of a twice-as-big matrix centered on the 3D image and give them the value $1/K$.
4. Fill the rest of the matrix using piecewise linear interpolation.

These weight maps W_k form a Lagrange interpolation basis and represent a kind of proximity map for each voxel of the image with the position P_k , shielded by the other positions $P_{j \neq k}$ and converging to $1/K$ for voxels far away from all of the K trackers.

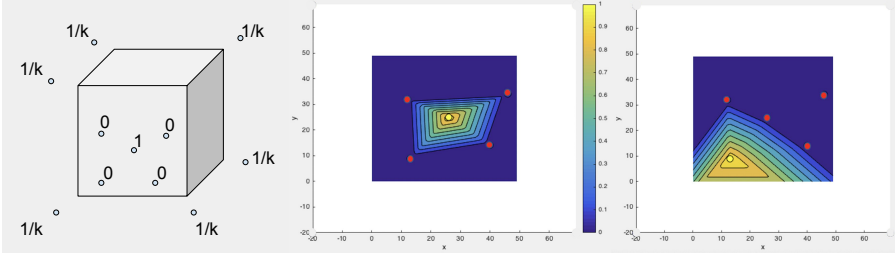


Figure 6.2: 3D schematic example of the weight map preparation (left). The position P_k is set to 1, the other tracker positions $P_{j \neq k}$ are set to 0 and the 8 corners of a larger cube outside the image are set to $1/k$ ($k=5$ in this example). The center and right images show example slices extracted from two different resulting 3D weight maps after filling by interpolation. The points $P_{j \neq k}$ are represented in red for visibility but have the value 0.

6.2.2 3D image deformation

Once the weight maps have been computed, each new frame $F_i(x, y)$ of the MRI sequence is used to create a 3DCT image (3DCT_i). First, each tracker T_k is used to compare the border position observed on the frame F_i with the border position observed on the 10 phases of the 4DCT_p inside the tracker as shown in figure 3. Then, a deformation field DT_k is computed for the tracker T_k using a combination of fields from the motion model fields D_n and a ratio r_k based on the tracked border position in this tracker. This can be done in two different ways, depending on whether the tracked border is inside or outside the range of positions represented in the motion model [Figure 6.3]. Note that the deformation fields DT_k depends on the current frame F_i but the dependency in i is omitted for the sake of conciseness.

Then, each field DT_k is multiplied by the weight map W_k and summed to create the final field DF_i to be applied to the midP image for the frame F_i . It gives a field that is locally equivalent to each of the DT_k fields on their corresponding trackers positions P_k and interpolated in-between. Formally it is

$$DF_i(x, y, z) = \sum_k DT_k(x, y, z)W_k(x, y, z), \quad (6.1)$$

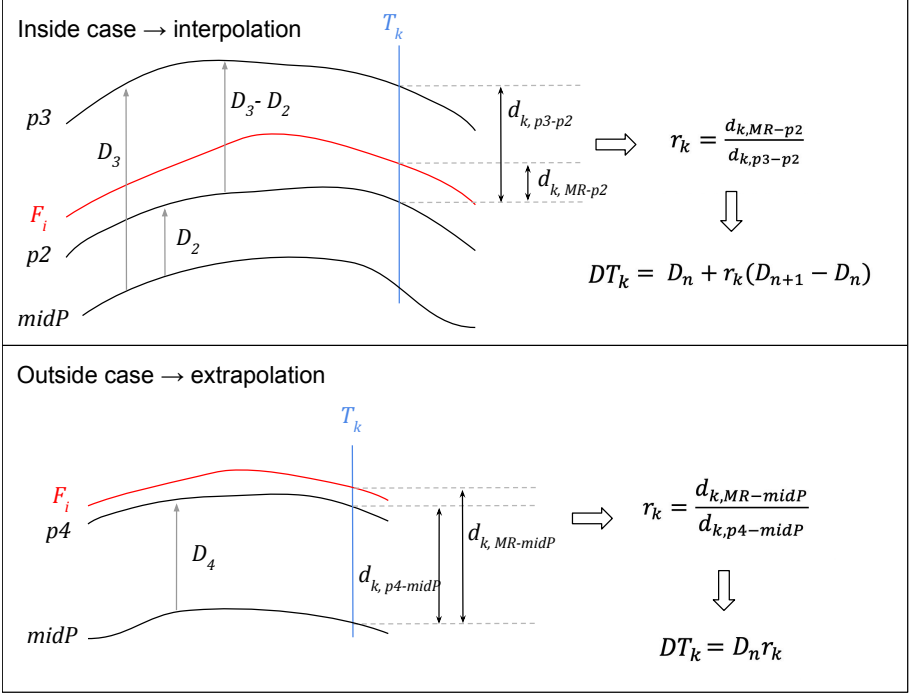


Figure 6.3: For each tracker T_k the position of the MR frame F_i is compared with the positions of the other phases pN and the midP image in this tracker. The ratio r_k is computed with the position differences d_k measured in the tracker T_k and then used to compute the field DT_k . There are two possible cases, interpolation when the F_i position is inside the range of the 4DCTp phases (top) or extrapolation when it is outside the range of the 4DCTp phases (bottom).

which implies

$$DF_i(x_k, y_k, z_k) = DT_k(x_k, y_k, z_k). \quad (6.2)$$

6.2.3 Material

The data come from thirteen patients treated for liver tumors by radiotherapy. MR images are True FISP sequences (Siemens Skyra 3T) of two interleaved slices (coronal and sagittal planes), acquired in treatment position with abdominal compression and centered on the tumor. The acquisition of both planes takes 550 ms, which make an acquisition frequency of 3.63 images per second because each frame is used independently. Images are 192x188 pixels wide with 1.82 mm/pixel in both directions. A 4DCT is also acquired the same day under the same conditions. This trial was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, approved by our local ethics committee (B403201628906).

6.3 Results

To evaluate if the method is able to reproduce the MRI motion, we first observe the difference between each frame F_i and the resulting 3DCT_i. The average of the absolute value of the difference between tracked border positions is computed for the tracker positions already used to create the images (UT for Used Tracker) and also for new trackers (NT) [Figure 6.4]. We can see that it is possible to reproduce the motion of the MRI at different tracker positions quite well, even if there were slight changes compared with the original motion model (in this case the patient breathing amplitude is lower than when the 4DCT_p was acquired) and if the patient breaths outside the range of the planning 4DCT_p (with a baseline shift for example). All tracker results for all patients are shown in Figure 6.5. The average of the difference between the reproduced motion and the MRI sequence is 0.93 mm (std: 0.66 mm) for UT (84 trackers) and 1.7 mm (std:1.14 mm) for NT (92 trackers).

During the creation of all the images of the 4DCT_c we also save the value of the 3D deformation applied to the tumor center. We analyzed the correlation between the motion of the tumor and the trackers

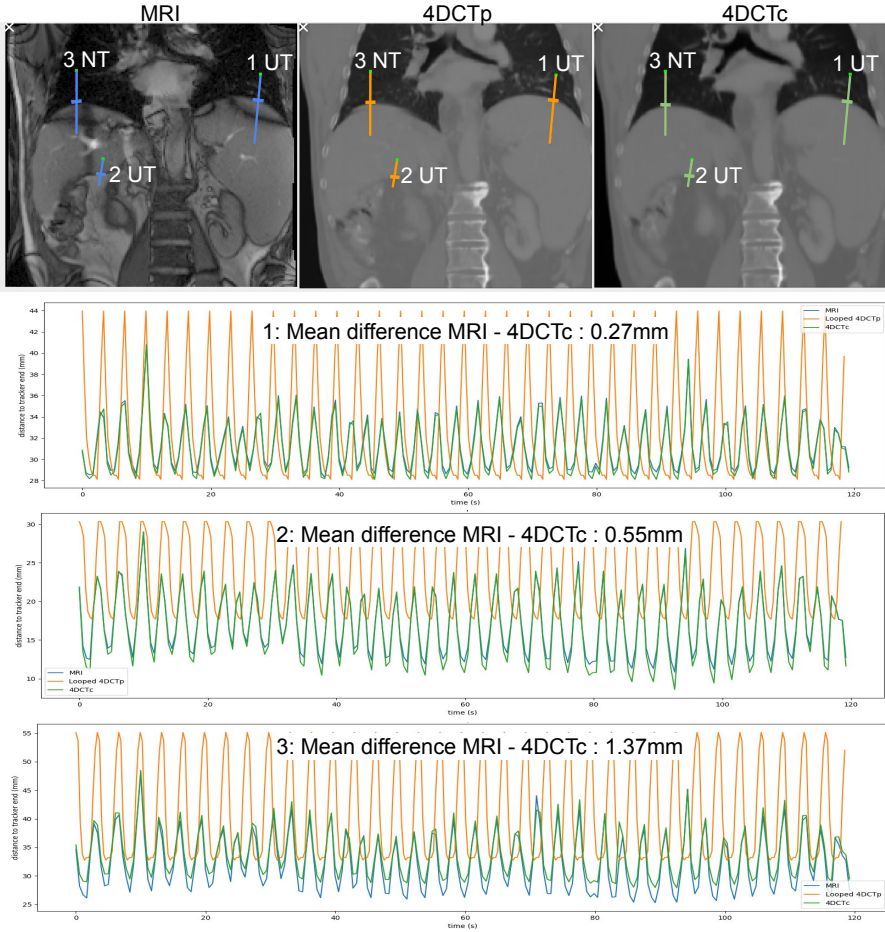


Figure 6.4: Example of motion tracked and computed differences between the MRI and the generated 4DCTc for two already used trackers (1 and 2) and one new tracker (3). The looped 4DCTp signal is also shown to show the baseline shift between the first tracker, where the MRI is always inside the range of the 4DCTp, and the other two where the MRI signals are outside the 4DCTp range about half of the time.

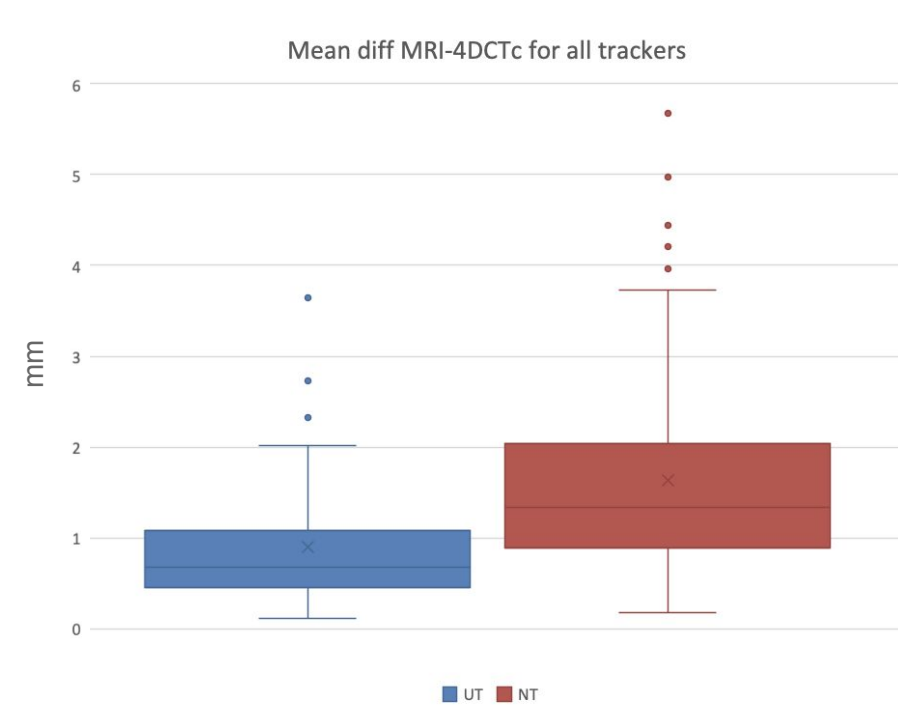


Figure 6.5: Box plot for all trackers, spit into Used (UT) and New (NT). The average of the absolute value of the difference between the reproduced motion and the MRI sequence is 0.93 mm (std: 0.66) for UT (81 trackers) and 1.7 mm (std:1.14) for NT (92 trackers).

Anatomic area	Average cross-correlation
Hepatic dome	0.71
Left diaphragmatic dome	0.71
Visceral liver surface	0.76
Right kidney	0.68
Skin	0.54

Table 6.1: Average cross-correlation between the motion of the tumor in the 4DCTc and the motion of trackers in the MRI, grouped by anatomical sites.

grouped by anatomic region (hepatic dome, left diaphragmatic dome, visceral liver surface, right kidney, skin, . . .). Except for the skin, which gave worse correlation results as expected [80], we did not find significant differences in correlation between anatomical areas to give guidelines regarding the ideal tracker positions [Table 6.1].

For six of the thirteen patients, where the tumor and the coronal and sagittal planes were not too close to the border of the liver, we were able to place trackers on the hepatic dome on either side of the sagittal and coronal planes' intersection. For those patients, we extracted the 3D motion of the tumor during the 4DCTc creation and compared the motion coming from the subsets of 3DCT images created using only the coronal slices and only the sagittal slices. We can see in the example in Figure 6.6 that both motions are well matched. If it is not the case, this can be a way to detect a baseline shift such as small rotations around a specific axis between the 4DCTp and the MRI.

We also tried to quantify the effect of breathing outside the range of the original 4DCTp on the quality of the reproduced motion, based on the fact that extrapolation can multiply small errors by the extrapolation factor $r_k > 1$. We computed the correlation coefficient between the percentage of MRI border position outside the range of the planning 4DCTp phases and the precision of the reproduced motion in the 4DCTc (mean difference MRI-4DCTc), but no significant correlation was found (Pearson coefficient of -0.16). Multiplying the fields DT_k with their respective weight maps W_k and adding them to the final field DF_i for an image of 340x360x60 voxels takes around 40 ms for each tracker with our unoptimized code on a decent laptop (2.9 GHz Intel Core i7

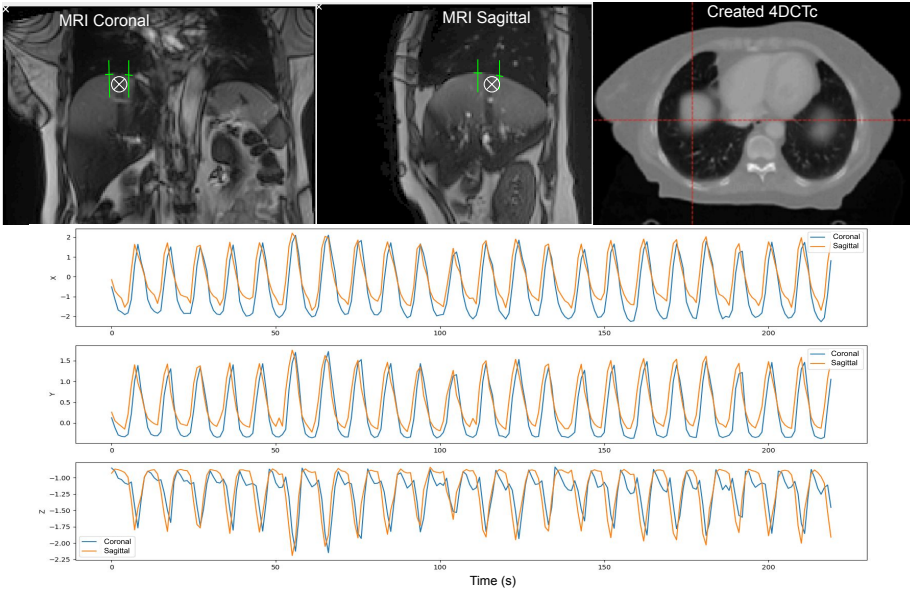


Figure 6.6: 3D motion of the tumor center (white cross) extracted from the created 4DCTc sequence and compared for images created using the coronal (blue signal) and sagittal (orange signal) slices separately. The 4DCTc from which the motion is extracted is created using, among other things the green trackers, placed on either side of the other plane, as shown on the MRI slices (top left and center).

7820HQ). The computation time scales linearly with the size of the area to deform.

6.4 Discussion

The errors of 0.93 mm for used trackers and 1.7 mm for new trackers using the local tuning of the fields show a significative improvement over the method of chapter 5 without local tuning, which resulted in a mean difference of 1.64 mm for used trackers and 2.2 mm for new trackers. It is on average an improvement of 43% for used trackers and 22% for new ones. Note that this border tracking method, while the fastest so far and giving immediate feedback on the results, relies on the use of manually placed trackers, which is not ideal to become a clinical solution. Increasing the speed of an automatic solution or combining the advantages of several options would be better and more realistic to go towards a real-time guiding solution.

Even if it is possible to reproduce a baseline shift occurring between the motion model creation and the online application, depending on whether trackers were placed in this area, we still recommend updating the 4D image and the motion model as regularly as possible. It can now be done using 4DMRI to reduce the imaging dose given during the treatment period [14].

While this method does add a step to existing methods relying on precomputed deformation fields, the added computation time can be quite short depending on the size of the image to deform and the number of different deformation fields to sum. While the area to deform can stay quite limited if only the path of the beam is used, it is important to consider if the goal is to apply it online.

6.5 Conclusion

This method used on top of existing methods to drive 3D motion models based on precomputed deformation fields improves the quality of the reproduced motion. It does add some computation time, which could be an issue in the case of real-time use, depending on the size of the area to deform.

Chapter 7

Discussion and Conclusion

7.1 Discussion

7.1.1 Motion model reliability

The use of motion models is necessary because the real-time 3D ground truth is currently not available. It is however possible to approximate the 3D situation based on the set of initial states and 2D real-time observations. Baseline shifts or change in the breathing pattern can happen between the model creation and the delivery of a fraction [27], making the model less precise or even obsolete. Ideally, the images and deformations in the model should be updated right before the delivery starts, with the patient already positioned for treatment. Our model based on Computed Tomography (CT) imaging modality is convenient for re-computing the dose deposition, but CT modality alone is not suitable to update the motion model as often as possible right before a treatment fraction. It would accumulate too much imaging dose if it has to be done every day for the entire treatment duration [47]. Fortunately, online MRI devices can also acquire 3D or 4D images that could be used to update the model using multi-modal registration or synthetic CT images creation [14, 62, 45, 51].

To detect intra-fraction baseline shifts, the initial tracking on the MRI slices can be used provided that the baseline shift occurs in this slice. For this purpose, choosing at least one slice position such as the

beam passes within the slice is recommended. To detect if the model is still valid and still manages to approximate the 3D motion despite a baseline shift, the tracking on the resulting 3D images coming out of the model can be used to get an immediate feedback. This can only validate the results in the available set of 2D slices which form the ground truth. The farther we go from these slices the less certainty we have, but we think it can be sufficient. The 2D slices can be chosen in any orientation and their position can be synchronized with the beam motion. The beam can still be covered well with a set of 2 or 3 slices that can be chosen orthogonal. Especially when using PBS where the spots size are lower than the slice thickness, we think it is a good approximation.

In its current state, the model uses a diffeomorphic field which ensure a realistic physical deformation in the sense that a tissue cannot appear or disappear, or pass through another (mirror effect). But there is no biomechanical constraints using the tissue properties to restrain the model in a certain range of deformation locally. For example in our method the liver could be deformed such as part of it ends up in the upper part of the thorax, crushing the lung in the process. An error as big as that did not occur in our results but as we can see in section 5.3, multiplying an error resulting in impossible deformations (in terms of tissue properties) can occur. A general regularization could be added to limit this effect (for example limit the deformation to a maximum value), or even a label-based regularization which uses the contours to define tissue-specific biomechanic rules such as the one used in registration methods based on biomechanical properties [39].

7.1.2 Manual tracker positioning

The trackers we use to measure breathing amplitude are robust to noise and work in real-time but can be difficult to place. The criterion to choose a good tracker position on a tissue border are the following:

- The tissue border must be visible on both MRI and CT modalities.
- Image artefact must be avoided on both MRI and CT modalities.
- The borders with high motion amplitude are preferred.

- The borders that are perpendicular to their motion are preferred.

The region with high motion amplitude and the borders perpendicular to their motion can be detected automatically without too much trouble with simple image processing operations. On the other hand, detecting if a border exists on both modalities and if there are no artefacts in this area is more challenging. We tried to develop a way to automate the tracker positioning or at least suggest to the user a set of trackers to choose from, but we did not find a good solution [83]. We realised that if the user had to choose the tracker from a suggested set anyway, that would not really save him much time.

We have therefore decided to keep the manual placement solution for the moment. With the software tool we created, we can immediately see if the tracking is working correctly or not on both modalities. With the experience I accumulated by placing a lot of trackers, I developed an intuition to find good areas to place them. Dr. Geneviève Van Ooteghem also used them to study non-invasive ventilation techniques [72, 75, 74] and she also got hold of it pretty quickly. However, intuition and experience is not a list of guidelines so this raises several questions regarding the transition to clinical practice:

- How to create the guidelines ?
- Does it require training ?
- Does it require a medical doctor ?
- Does it require a validation of the trackers before delivery ?

In a way it is similar to the contouring process, which brings issues like inter-observers variability or personal habits. This is a limitation of our method and ideally this part should be replaced by an automatic solution to be considered a good option for clinical practice.

7.1.3 Real-time uses

The definition of real-time process can vary depending on the application, field or convention. We will use the following definition : *A real-time process is generally one that happens in defined time steps of*

*maximum duration and fast enough to affect the environment in which it occurs, such as inputs to a computing system.*¹ Using this, we will discuss different uses of our method and what *real-time* means in each case.

1. Retrospective dose accumulation tool based on real-time MRI.

In order to be used to recompute the fraction dose retrospectively, only the MRI acquisition needs to be fast enough to capture any irregularities in the breathing pattern. The method presented here, including the motion tracking, can simply be used afterwards off-line. Such use can make it possible to recalculate and accumulate the dose delivered between each fraction for an adaptive strategy (cf. chapter 1).

2. Real-time anatomy-based verification or guiding tool.

This second usage possibility is during a fraction delivery. Monitoring the motion using the 2D slices in order to be able to either raise a flag if an anomaly is detected or guide a treatment using a gating or tracking strategy. In this case, the tissue interface tracking and breathing state evaluation have to be processed fast enough such as not too much motion occurred between the image acquisition and the action on the beam (ON/OFF switch or displacement). This is not an issue as these steps take only a few milliseconds with our method. The main issue in this case is the MRI acquisition and reconstruction time. It has been reported to be in the best case around 150 ms on an MR-Linac [12] For this real-time use our method does not bring a particular advantage, as the 3D motion is not necessary and other methods already exists to use gating on MR Linacs [102]. A retrospective dose accumulation can still be added after a fraction using everything that was recorded during the fraction (the 2D slices but also the delivery timings and beam position).

3. Real-time dose-based verification or guiding tool.

¹<https://en.wikipedia.org/wiki/Real-time>

This is where things gets tricky. Using it as a verification or guiding tool based on the delivered dose to stop or guide the treatment if some criterion about the given dose is reached. In this case the dose must be computed continuously and accumulated. It means the motion must be tracked on the 2D MRI image, passed to the motion model where the 3DCT image has to be created using deformation, and the dose delivered during the current image timeframe must be computed on this 3DCT image. Achieving this in the time frame between 2 MRI slices (around 350 ms) seems difficult for now. But if a small latency of a couple of seconds is acceptable, such a real-time dose delivery observation tool might be possible. Fast dose computation methods already exists [35, 63] and may become even faster in the future.

Additionally to these real-time use, another limitation must be considered. As mentioned earlier in section 7.1.1, ideally the motion model should be updated in room before each fraction. However for the complete workflow to be possible online in reasonable time, other steps must also be accelerated. Not only the model update (image acquisition, non-rigid registration and midP image creation), but also contouring and treatment re-planning speed need to be considered. The patient will have to stay in treatment position through all these steps. Progress in these areas is steady with the arrival of automatic contouring [59, 42, 99], ultra fast planning [35, 63] and in general the steady increase of computation power. It is only when the complete workflow will be achievable in a reasonable time that it will be possible to update the motion model for each fraction.

7.1.4 Other perspectives

If MR-Linacs keep their promises and that efficient real-time tracking methods arrive in clinical routine, it can be argued that protontherapy will lose popularity for mobile tumors. It has the potential to deliver better dose distribution but compared to photons with a brand new aiming method, I would have difficulties trusting a blind proton. I certainly hope the development of hybrid MRI-Protons keeps progressing in the coming years to balance the weapons and see the protons unlock their potential.

7.2 Conclusion

Online MRI has the potential to bring external beam radiation therapy of mobile tumors to the next level by strongly reducing security margins. It is the only efficient non-invasive method with soft tissue contrast sufficient to distinguish most tumors. With the possibility of 3D or 4D acquisition right before a treatment fraction and high frequency 2D acquisition during delivery, it combines everything that is necessary to build an efficient 3D motion model-based tracking method. On top of that, it is still a young field and will probably keep progressing in the following years, both in image quality and acquisition speed. Most of the uncertainties and issues that cause healthy tissues to be hit unnecessarily with current treatments are due to the fact that we do not see what we treat. With non-invasive methods, the target position can only be approximated based on outdated or low contrast images. The target coverage is assured by using huge margins to reduce the risk of missing part of it to an acceptable threshold. As a result and as shown in chapter 4, the state of the art methods we use today sometimes only hit the target with around 25% of rays. There is a need for real-time tracking solutions that would allow a reduction or suppression of motion margins by continuously following the target with the beam. In this thesis, we develop a way to derive a good approximation of the 3D motion from 2D cine-MRI slices in real-time, such as it could be used to observe in real-time or nearly real-time a treatment delivery.

We started by developing a tool to observe a treatment delivery. It can be used to compute simple statistics such as the fraction of spots delivered towards the target. With this we also developed a method to recompute the range and dose of PBS spots while considering breathing pattern observed on the dynamic images and not simply an average breathing period. With the method presented in chapter 4 it could be achieved only partially because we only had access to the motion happening inside the chosen MRI slices. On top of that, we also used for this first patient a manually contoured target on the MRI slices, which in practice would need to be replaced by an efficient real-time tracking method on 2D slices [13]. The results we obtained from these two experiments were interesting and informative. The method was fast enough to be used in real-time if we suppose a fast range and dose

computation as well. But it was not sufficient to really compare different treatment strategies. To achieve that, 3D volumes are needed because some of the OAR's constraints can be local. It is only by having the full volume that it is possible to check them.

The next step was then to find a way to expand the motion observed in 2D to a 3D motion, but still in real-time. Motion models seemed an appropriate way because the preparation of the model can be done previous to the treatment, and only the application of the model has to be fast. At this time scale, applying a deformation to an image is time consuming, meaning getting the observation to drive the model had to be fast to compensate. We developed a simple interface tracking method that gives this information nearly instantaneously, but requires a manual intervention before treatment in its current state. By using the same method also after the deformation of the image, it can give an immediate feedback on the quality of the reproduced motion and detect if the model is still valid. By using multiple trackers it was possible to create an average breathing state if one tracker detected a different state than another. This way, the approximation error is spread evenly on the entire image, but it is not really possible to create an image which contains different breathing states at different locations.

An additional step was then added to the motion model before the image is deformed. This step combines the breathing states detected by multiple trackers by using a weighted sum of deformation fields. The resulting field allows to represent the exact breathing state detected by each tracker on their respective location, and interpolate the breathing states in between. This adds computation time to the process but improves the precision of the previous method and can also be applied to any motion model method which uses precomputed deformation fields.

We developed a robust solution towards online 3D tracking and on-line treatment verification. Of course, a lot of research must be performed to use it in clinical practice but I think this is one of the path we can take to keep improving the radiation therapy field and save more lives.

Bibliography

- [1] *Health at a Glance: Europe 2018*. OECD, 11 2018.
- [2] Sahaja Acharya, Benjamin W Fischer-Valuck, Rojano Kashani, Parag Parikh, Deshan Yang, Tianyu Zhao, Olga Green, Omar Wooten, H Harold Li, Yanle Hu, Vivian Rodriguez, Lindsey Olsen, Clifford Robinson, Jeff Michalski, Sasa Mutic, and Jeffrey Olsen. Online magnetic resonance image guided adaptive radiation therapy: First clinical applications. *International journal of radiation oncology, biology, physics*, 94:394–403, 2015.
- [3] James M. Balter, J. Nelson Wright, Laurence J. Newell, Barry Friemel, Steven Dimmer, Yuki Cheng, John Wong, Edward Vertatschitsch, and Timothy P. Mate. Accuracy of a wireless localization system for radiotherapy. *International Journal of Radiation Oncology*Biology*Physics*, 61, 3 2005.
- [4] Neal K Bangerter, Brian A Hargreaves, Shreyas S Vasanawala, John M Pauly, Garry E Gold, and Dwight G Nishimura. Analysis of multiple-acquisition ssfp. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 51(5):1038–1047, 2004.
- [5] Gillian C. Barnett, Catherine M. L. West, Alison M. Dunning, Rebecca M. Elliott, Charlotte E. Coles, Paul D. P. Pharoah, and Neil G. Burnet. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nature Reviews Cancer*, 9, 2 2009.
- [6] A. Sam Beddar, Kristofer Kainz, Tina Marie Briere, Yoshikazu Tsunashima, Tinsu Pan, Karl Prado, Radhe Mohan, Michael

- Gillin, and Sunil Krishnan. Correlation between internal fiducial tumor motion and external marker motion for liver tumors imaged with 4d-ct. *International Journal of Radiation Oncology*Biology*Physics*, 67, 2 2007.
- [7] R. Berbeco, S. Nishioka, H. Shirato, G. Chen, and S. Jiang. Residual motion of lung tumors in gated radiotherapy with external respiratory surrogates. *Medical Physics*, 32:2124, 2005.
- [8] Christoph Bert, Sven O. Grözinger, and Eike Rietzel. Quantification of interplay effects of scanned particle beams and moving targets. *Physics in Medicine and Biology*, 53:2253–2265, 5 2008.
- [9] J Bertholet, H Wan, J Toftegaard, M L Schmidt, F Chotard, P J Parikh, and P R Poulsen. Fully automatic segmentation of arbitrarily shaped fiducial markers in cone-beam ct projections. *Physics in Medicine and Biology*, 62, 2 2017.
- [10] Jenny Bertholet, Antje Knopf, Björn Eiben, Jamie McClelland, Alexander Grimwood, Emma Harris, Martin Menten, Per Poulsen, Doan Trang Nguyen, Paul Keall, and Uwe Oelfke. Real-time intrafraction motion monitoring in external beam radiotherapy. *Physics in Medicine and Biology*, 64, 8 2019.
- [11] Judit Boda-Heggemann, Antje-Christin Knopf, Anna Simeonova-Chergou, Hansjörg Wertz, Florian Stieler, Anika Jahnke, Lennart Jahnke, Jens Fleckenstein, Lena Vogel, Anna Arns, Manuel Blessing, Frederik Wenz, and Frank Lohr. Deep inspiration breath hold—based radiation therapy: A clinical review. *International Journal of Radiation Oncology*Biology*Physics*, 94, 3 2016.
- [12] P. T.S. Borman, R. H.N. Tijssen, C. Bos, C. T.W. Moonen, B. W. Raaymakers, and M. Glitzner. Characterization of imaging latency for real-time mri-guided radiotherapy. *Physics in Medicine and Biology*, 63, 8 2018.
- [13] Alexandra E Bourque, Stéphane Bedwani, Jean-François Carrier, Cynthia Ménard, Pim Borman, Clemens Bos, Bas W Raaymakers, Nikolai Mickevicius, Eric Paulson, and Rob HN Tijssen.

- Particle filterbased target tracking algorithm for magnetic resonance-guided respiratory compensation: Robustness and accuracy assessment. *Radiation Oncology Biology*, 100:325–334, 2018.
- [14] Dirk Boye, Tony Lomax, and Antje Knopf. Mapping motion from 4d-mri to 3d-ct for use in 4d dose calculations: A technical feasibility study. *Medical Physics*, 2013.
- [15] Lau Brix, Steffen Ringgaard, Thomas Sangild Sørensen, and Per Rugaard Poulsen. Three-dimensional liver motion tracking using real-time two-dimensional mri. *Medical Physics*, 41, 4 2014.
- [16] Gregory Buti, Kevin Souris, Ana Maria Barragán Montero, John Aldo Lee, and Edmond Sterpin. Towards fast and robust 4d optimization for moving tumors with scanned proton therapy. *Medical Physics*, 46:5434–5443, 12 2019.
- [17] HY Carr. Steady-state free precession in nuclear magnetic resonance. *Physical Review*, 112(5):1693, 1958.
- [18] Robert B. Case, Jan-Jakob Sonke, Douglas J. Moseley, John Kim, Kristy K. Brock, and Laura A. Dawson. Inter- and intrafraction variability in liver position in non-breath-hold stereotactic body radiotherapy. *International Journal of Radiation Oncology*Biophysics*, 75, 9 2009.
- [19] Stephen Chin, Cynthia L. Eccles, Alan McWilliam, Robert Chuter, Emma Walker, Philip Whitehurst, Joseph Berresford, Marcel Van Herk, Peter J. Hoskin, and Ananya Choudhury. Magnetic resonance-guided radiation therapy: A review, 2019.
- [20] Tiago da Silva Jornada, Camila Hitomi Murata, and Regina Bitelli Medeiros. Influence of partial k-space filling on the quality of magnetic resonance images. *Radiologia Brasileira*, 49, 6 2016.
- [21] Damien Dasnoy-Sumell. 4dct co-synchronized to real-time dynamic mri. international conference on the use of computers in radiation therapy annual symposium 2019, montréal, canada.
- [22] Damien Dasnoy-Sumell. Proton therapy pbs plan real-time simulation and visualisation tool. ulb-cancer research center annual symposium 2017, brussels, belgium.

- [23] Damien Dasnoy-Sumell. Towards real-time pbs dose accumulation observation using dynamic mri. magnetic resonance in radiation therapy annual symposium 2018, utrecht, netherlands.
- [24] Damien Dasnoy-Sumell. Towards real-time proton range verification using dynamic mri. 4d treatment planning workshop annual symposium 2017, vienna, austria.
- [25] Damien Dasnoy-Sumell, Kevin Souris, G. Van Ooteghem, and Benoit Macq. Continuous real time 3d motion reproduction using dynamic mri and precomputed 4dct deformation fields. *Journal of Applied Clinical Medical Physics*, 21:236–248, 8 2020.
- [26] Anagha Deshmane, Vikas Gulani, Mark A. Griswold, and Nicole Seiberlich. Parallel mr imaging. *Journal of Magnetic Resonance Imaging*, 2012. NULL.
- [27] Jennifer Dhont, Jef Vandemeulebroucke, Manuela Burghilea, Kenneth Poels, Tom Depuydt, Robbe Van Den Begin, Cyril Jaudet, Christine Collen, Benedikt Engels, Truus Reynders, Marlies Bousaer, Thierry Gevaert, Mark De Ridder, Dirk Verellen, and Ziekenhuis Leuven. The long- and short-term variability of breathing induced tumor motion in lung and liver over the course of a radiotherapy treatment. *Radiotherapy and Oncology*, 2017.
- [28] Cynthia L. Eccles, Ritesh Patel, Anna K. Simeonov, Gina Lockwood, Masoom Haider, and Laura A. Dawson. Comparison of liver tumor motion with and without abdominal compression using cine-magnetic resonance imaging. *International Journal of Radiation Oncology Biology Physics*, 79:602–608, 2 2011.
- [29] Biagio Gino Fallone. The rotating biplanar linac–magnetic resonance imaging system. *Seminars in Radiation Oncology*, 24, 7 2014.
- [30] Hadi J. Fayad, Christian Buerger, Charalampos Tsoumpas, Catherine Cheze-Le-Rest, and Dimitris Visvikis. A generic respiratory motion model based on 4d mri imaging and 2d image navigators. pages 4058–4061, 2012.

- [31] W Fledelius, E Worm, M Høyer, C Grau, and P R Poulsen. Real-time segmentation of multiple implanted cylindrical liver markers in kilovoltage and megavoltage x-ray images. *Physics in Medicine and Biology*, 59, 6 2014.
- [32] Noemi Garau, Riccardo Via, Giorgia Meschini, Danny Lee, Paul Keall, Marco Riboldi, Guido Baroni, and Chiara Paganelli. A roi-based global motion model established on 4dct and 2d cine-mri data for mri-guidance in radiation therapy. *Physics in Medicine and Biology*, 64, 2 2019.
- [33] Samuel Goossens, Frédéric Senny, John Aldo Lee, Guillaume Janssens, and Xavier Geets. Assessment of tumor motion reproducibility with audio-visual coaching through successive 4d ct sessions. *Journal of Applied Clinical Medical Physics*, 15:47–56, 2014.
- [34] Clemens Grassberger, Stephen Dowdell, Antony Lomax, Greg Sharp, James Shackleford, Noah Choi, Henning Willers, and Harald Paganetti. Motion interplay as a function of patient parameters and spot size in spot scanning proton therapy for lung cancer. *International Journal of Radiation Oncology Biology Physics*, 2013.
- [35] M De Greef, J Crezee, J C Van Eijk, R Pool, A Bel, M De Greef, J Crezee, J C Van Eijk, R Pool, and A Bel. Accelerated ray tracing for radiotherapy dose calculations on a gpu. 4095, 2013.
- [36] Alexander Grimwood, Helen A. McNair, Tuathan P. O’Shea, Stephen Gilroy, Karen Thomas, Jeffrey C. Bamber, Alison C. Tree, and Emma J. Harris. In vivo validation of elekta’s clarity autoscan for ultrasound-based intrafraction motion estimation of the prostate during radiation therapy. *International Journal of Radiation Oncology*Biology*Physics*, 102, 11 2018.
- [37] Matthias Guckenberger, Reinhart A. Sweeney, Juergen Wilbert, Thomas Krieger, Anne Richter, Kurt Baier, Gerd Mueller, Otto Sauer, and Michael Flentje. Image-guided radiotherapy for liver cancer using respiratory-correlated computed tomography and cone-beam computed tomography. *International Journal of Radiation Oncology*Biology*Physics*, 71, 5 2008.

- [38] Alexander R. Guimaraes, John E. Kirsch, Ravi T. Seethamraju, Susie Y. Huang, Peter F. Hahn, and Pritesh Patel. Body mr imaging: Artifacts, k-space, and solutions. *RadioGraphics*, 2015.
- [39] Lianghao Han, Hua Dong, Jamie R. McClelland, Liangxiu Han, David J. Hawkes, and Dean C. Barratt. A hybrid patient-specific biomechanical model based image registration method for the motion estimation of lungs. *Medical Image Analysis*, 39:87 – 100, 2017.
- [40] Wendy Harris, Lei Ren, Jing Cai, You Zhang, Zheng Chang, and Fang Fang Yin. A technique for generating volumetric cine-magnetic resonance imaging. *International Journal of Radiation Oncology Biology Physics*, 95:844–853, 6 2016.
- [41] J Hartman, C Kontaxis, G H Bol, S J Frank, J J W Lagendijk, M Van Vulpen, and B W Raaymakers. Dosimetric feasibility of intensity modulated proton therapy in a transverse magnetic field of dosimetric feasibility of intensity modulated proton therapy in a transverse magnetic field of 1.5 t. *Phys. Med. Biol*, 60, 2015.
- [42] Mohammad Hesam Hesamian, Wenjing Jia, Xiangjian He, and Paul Kennedy. Deep learning techniques for medical image segmentation: Achievements and challenges. *Journal of Digital Imaging*, 32, 8 2019.
- [43] Guillaume Janssens, Laurent Jacques, Jonathan Orban De Xivry, Xavier Geets, and Benoit MacQ. Diffeomorphic registration of images with variable contrast enhancement. *International Journal of Biomedical Imaging*, 2011.
- [44] R Joel L Ehman and Felmlee. Adaptive technique for high definition mr imaging of moving structures. *Radiology*, 1989.
- [45] Emily Johnstone, Jonathan J. Wyatt, Ann M. Henry, Susan C. Short, David Sebag-Montefiore, Louise Murray, Charles G. Kelly, Hazel M. McCallum, and Richard Speight. A systematic review of synthetic ct generation methodologies for use in mri-only radiotherapy. *International Journal of Radiation Oncology*Biology*Physics*, 2017.

- [46] Yixiu Kang, Xiaodong Zhang, Joe Y. Chang, He Wang, Xiong Wei, Zhongxing Liao, Ritsuko Komaki, James D. Cox, Peter A. Balter, Helen Liu, X. Ronald Zhu, Radhe Mohan, and Lei Dong. {A figure is presented}4d proton treatment planning strategy for mobile lung tumors. *International Journal of Radiation Oncology Biology Physics*, 67:906–914, 3 2007.
- [47] Paul J. Keall, Gig S. Mageras, James M. Balter, Richard S. Emery, Kenneth M. Forster, Steve B. Jiang, Jeffrey M. Kapatoes, Daniel A. Low, Martin J. Murphy, Brad R. Murray, Chester R. Ramsey, Marcel B. Van Herk, S. Sastry Vedam, John W. Wong, and Ellen Yorke. The management of respiratory motion in radiation oncology report of aapm task group 76a). *Medical Physics*, 33, 9 2006.
- [48] Kei Kitamura, Hiroki Shirato, Yvette Seppenwoolde, Tadashi Shimizu, Yoshihisa Kodama, Hideho Endo, Rikiya Onimaru, Makoto Oda, Katsuhisa Fujita, Shinichi Shimizu, and Kazuo Miyasaka. Tumor location, cirrhosis, and surgical history contribute to tumor movement in the liver, as measured during stereotactic irradiation using a real-time tumor-tracking radiotherapy system. *International Journal of Radiation Oncology Biology Physics*, 56:221–228, 5 2003.
- [49] Stefan Klein, Marius Staring, Keelin Murphy, Max A. Viergever, and Josien P.W. Pluim. Elastix: A toolbox for intensity-based medical image registration. *IEEE Transactions on Medical Imaging*, 29:196–205, 1 2010.
- [50] Antje Christin Knopf, Dirk Boye, Antony Lomax, and Shininchi Mori. Adequate margin definition for scanned particle therapy in the incidence of intrafractional motion. *Physics in Medicine and Biology*, 58:6079–6094, 9 2013.
- [51] Lauri Koivula, Leonard Wee, and Juha Korhonen. Feasibility of mri-only treatment planning for proton therapy in brain and prostate cancers: Dose calculation accuracy in substitute ct images. *Medical Physics*, 2016.

- [52] Saban Kurucay, Petra Schmalbrock, Donald W Chakeres, and Paul J Keller. A segment-interleaved motion-compensated acquisition in the steady state (simcast) technique for high resolution imaging of the inner ear. *Journal of Magnetic Resonance Imaging*, 7(6):1060–1068, 1997.
- [53] Martin Lachaine and Tony Falco. Intrafractional prostate motion management with the clarity autoscan system, 2013.
- [54] Jan J W Lagendijk, Bas W. Raaymakers, Alexander J E Raaijmakers, Johan Overweg, Kevin J. Brown, Ellen M. Kerkhof, Richard W. van der Put, Björn Hårdemark, Marco van Vulpen, and Uulke A. van der Heide. Mri/linac integration. *Radiotherapy and Oncology*, 86:25–29, 1 2008.
- [55] Jan J W Lagendijk, Bas W. Raaymakers, and Marco van Vulpen. The magnetic resonance imaging-linac system, 2014.
- [56] Zhiwen Liang, Hongyuan Liu, Jun Xue, Bin Hu, Bin Zhu, Qin Li, Sheng Zhang, and Gang Wu. Evaluation of the intra- and interfractional tumor motion and variability by fiducial-based real-time tracking in liver stereotactic body radiation therapy. *Journal of Applied Clinical Medical Physics*, 19, 5 2018.
- [57] Liyong Lin, Kevin Souris, Minglei Kang, Adam Glick, Haibo Lin, Sheng Huang, Kristin Stützer, Guillaume Janssens, Edmond Sterpin, John A. Lee, Timothy D. Solberg, James E. McDonough, Charles B. Simone, and Edgar Ben-Josef. Evaluation of motion mitigation using abdominal compression in the clinical implementation of pencil beam scanning proton therapy of liver tumors:. *Medical Physics*, 44:703–712, 2 2017.
- [58] G. P. Liney, B. Dong, J. Begg, P. Vial, K. Zhang, F. Lee, A. Walker, R. Rai, T. Causer, S. J. Alnaghy, B. M. Oborn, L. Holloway, P. Metcalfe, M. Barton, S. Crozier, and P. Keall. Technical note: Experimental results from a prototype high-field inline mri-linac. *Medical Physics*, 43, 8 2016.
- [59] Geert Litjens, Thijs Kooi, Babak Ehteshami Bejnordi, Arnaud Arindra Adiyoso Setio, Francesco Ciompi, Mohsen Ghafoorian,

- Jeroen A.W.M. van der Laak, Bram van Ginneken, and Clara I. Sánchez. A survey on deep learning in medical image analysis. *Medical Image Analysis*, 42, 12 2017.
- [60] T. E. Marchant, A. Skalski, and B. J. Matuszewski. Automatic tracking of implanted fiducial markers in cone beam ct projection images. *Medical Physics*, 39, 2 2012.
- [61] Lawrence B Marks, Ellen D Yorke, Andrew Jackson, Randall K Ten Haken, Louis S Constine, Avraham Eisbruch, Søren M Bentzen, Jiho Nam, and Joseph O Deasy. Use of normal tissue complication probability models in the clinic. *International journal of radiation oncology, biology, physics*, 76:S10–9, 3 2010.
- [62] Matteo Maspero, Mark H. F. Savenije, Anna M. Dinkla, Peter R. Seevinck, Martijn P. W. Intven, Ina M. Jurgensliemk-Schulz, Linda G. W. Kerkmeijer, and Cornelis A. T. van den Berg. Dose evaluation of fast synthetic-ct generation using a generative adversarial network for general pelvis mr-only radiotherapy. 2018.
- [63] Michael Matter, Lena Nenoff, Gabriel Meier, Damien C. Weber, Antony J. Lomax, and Francesca Albertini. Intensity modulated proton therapy plan generation in under ten seconds. *Acta Oncologica*, 58:1435–1439, 10 2019.
- [64] Jamie R. McClelland, Marc Modat, Simon Arridge, Helen Grimes, Derek D’Souza, David Thomas, Dylan O. Connell, Daniel A. Low, Evangelia Kaza, David J. Collins, Martin O. Leach, and David J. Hawkes. A generalized framework unifying image registration and respiratory motion models and incorporating image reconstruction, for partial image data or full images. *Physics in Medicine and Biology*, 62:4273–4292, 5 2017.
- [65] Helen A. McNair, Juliet Brock, J. Richard N. Symonds-Tayler, Sue Ashley, Sally Eagle, Philip M. Evans, Anthony Kavanagh, Niki Panakis, and Michael Brada. Feasibility of the use of the active breathing co ordinator™ (abc) in patients receiving radical radiotherapy for non-small cell lung cancer (nscl). *Radiotherapy and Oncology*, 93, 12 2009.

- [66] M Moteabbed, J Schuemann, H Paganetti, and) J Schuemann. Dosimetric feasibility of real-time mri-guided proton therapy. *Medical Physics Med. Phys.*, 41, 2014.
- [67] S. Mutic, D. Low, T. Chmielewski, G. Fought, G. Gerganov, M. Hernandez, I. Kawrakow, E. Kishawi, G. Kuduvalli, A. Sharma, S. Shvartsman, J. Tabachnik, R. Kashani, O.L. Green, and J.F. Dempsey. The design and implementation of a novel compact linear accelerator-based magnetic resonance imaging-guided radiation therapy (mr-igrt) system. *International Journal of Radiation Oncology*Biography*Physics*, 96, 10 2016.
- [68] Christopher Nelson, George Starkschall, Peter Balter, Rodolfo C. Morice, Craig W. Stevens, and Joe Y. Chang. Assessment of lung tumor motion and setup uncertainties using implanted fiducials. *International Journal of Radiation Oncology Biology Physics*, 67:915–923, 3 2007.
- [69] Henrik D. Nissen and Ane L. Appelt. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. *Radiotherapy and Oncology*, 106, 1 2013.
- [70] B M Oborn, S Dowdell, P E Metcalfe, S Crozier, R Mohan, and P J Keall. Proton beam deflection in mri fields: Implications for mri-guided proton therapy. *Medical Physics*, 42:2113–2124, 2015.
- [71] Bradley M. Oborn, Stephen Dowdell, Peter E. Metcalfe, Stuart Crozier, Radhe Mohan, and Paul J. Keall. Future of medical physics: Real-time mri-guided proton therapy: Real-time. *Medical Physics*, 44:e77–e90, 8 2017.
- [72] G. Van Ooteghem, D. Dasnoy-Sumell, and X. Geets. Réduction des variations pendant et entre les fractions respiro-induites : le potentiel de la ventilation mécanique orientée vers les stratégies de mitigation du mouvement pour l’irradiation des tumeurs thoraciques ou abdominales. *Cancer/Radiothérapie*, 23, 10 2019.
- [73] Geneviève Van Ooteghem, Damien Dasnoy-Sumell, Maarten Lambrecht, Grégory Reyckler, Giuseppe Liistro, Edmond Sterpin, and

- Xavier Geets. Mechanically-assisted non-invasive ventilation: A step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy. *Radiotherapy and Oncology*, 133:132–139, 4 2019.
- [74] Geneviève Van Ooteghem, Damien Dasnoy-Sumell, Maarten Lambrecht, Grégory Reyckler, Giuseppe Liistro, Edmond Sterpin, and Xavier Geets. Mechanically-assisted non-invasive ventilation: A step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy. *Radiotherapy and Oncology*, 133, 4 2019.
- [75] Geneviève Van Ooteghem, Damien Dasnoy-Sumell, John Aldo Lee, and Xavier Geets. Mechanically-assisted and non-invasive ventilation for radiation therapy: A safe technique to regularize and modulate internal tumour motion. *Radiotherapy and Oncology*, 141, 12 2019.
- [76] A Oppelt, R Graumann, H Barfuss, H Fischer, W Hartl, W Schajor, et al. Fisp—a new fast mri sequence. *Electromedica*, 54(1):15–18, 1986.
- [77] Amir M. Owringi, Peter B. Greer, and Carri K. Glide-Hurst. Mri-only treatment planning: Benefits and challenges. *Physics in Medicine and Biology*, 2018.
- [78] C. Paganelli, S. Portoso, N. Garau, G. Meschini, R. Via, G. Buizza, P. Keall, M. Riboldi, and G. Baroni. Time-resolved volumetric mri in mri-guided radiotherapy: An in silico comparative analysis. *Physics in Medicine and Biology*, 64, 9 2019.
- [79] Chiara Paganelli, Danny Lee, John Kipritidis, Brendan Whelan, Peter B. Greer, Guido Baroni, Marco Riboldi, and Paul Keall. Feasibility study on 3d image reconstruction from 2d orthogonal cine-mri for mri-guided radiotherapy. *Journal of Medical Imaging and Radiation Oncology*, 62:389–400, 6 2018.
- [80] Chiara Paganelli, Matteo Seregini, Giovanni Fattori, Paul Summers, Massimo Bellomi, Guido Baroni, and Marco Riboldi. Magnetic resonance imaging-guided versus surrogate-based motion

- tracking in liver radiation therapy: A prospective comparative study. *International Journal of Radiation Oncology Biology Physics*, 91:840–848, 3 2015.
- [81] Justin C Park, Sung Ho Park,) Jong, Hoon Kim, Min Yoon, Si Yeol Song, Zhaowei Liu, Bongyong Song, Kevin Kauwelo, Matthew J Webster, Ajay Sandhu, Loren K Mell, Steve B Jiang, Arno J Mundt, and William Y Song. Liver motion during cone beam computed tomography guided stereotactic body radiation therapy. 2012.
- [82] Seyoun Park, Rana Farah, Steven M. Shea, Erik Tryggstad, Russell Hales, and Junghoon Lee. Simultaneous tumor and surrogate motion tracking with dynamic mri for radiation therapy planning. *Physics in Medicine and Biology*, 63, 1 2018.
- [83] Romain Pattyn. Automatic mri-ct region matching for motion tracking using computer vision. Master’s thesis, UCL - Ecole polytechnique de Louvain, 2020.
- [84] Pr. Frank Peeters. *Imagerie medicale - GBIO2050. Chapitre 4 : Magnetic resonance imaging*. Universite Catholique de Louvani, 2015.
- [85] Robert A. Pooley. Fundamental physics of mr imaging. *Radio-graphics*, 25:1087–1099, 2005.
- [86] B. W. Raaymakers, I. M. Jürgenliemk-Schulz, G. H. Bol, M. Glitzner, A. N.T.J. Kotte, B. Van Asselen, J. C.J. De Boer, J. J. Bluemink, S. L. Hackett, M. A. Moerland, S. J. Woodings, J. W.H. Wolthaus, H. M. Van Zijp, M. E.P. Philippens, R. Tjssen, J. G.M. Kok, E. N. De Groot-Van Breugel, I. Kiekebosch, L. T.C. Meijers, C. N. Nomden, G. G. Sikkes, P. A.H. Doornaert, W. S.C. Eppinga, N. Kasperts, L. G.W. Kerkmeijer, J. H.A. Tersteeg, K. J. Brown, B. Pais, P. Woodhead, and J. J.W. Lagendijk. First patients treated with a 1.5 t mri-linac: Clinical proof of concept of a high-precision, high-field mri guided radiotherapy treatment. *Physics in Medicine and Biology*, 62:L41–L50, 11 2017.

- [87] Marco Riboldi, Roberto Orecchia, and Guido Baroni. Real-time tumour tracking in particle therapy: technological developments and future perspectives. *The Lancet Oncology*, 13, 9 2012.
- [88] Eike Rietzel and Christoph Bert. Respiratory motion management in particle therapy. *Medical Physics*, 37:449–460, 2010.
- [89] IMAIOS SAS. Mri step-by-step, interactive course on magnetic resonance imaging. <https://www.imaios.com/fr/e-Cours/e-MRI>, visited in January 2021.
- [90] Klaus Scheffler and Stefan Lehnhardt. Principles and applications of balanced ssfp techniques. *European radiology*, 13(11):2409–2418, 2003.
- [91] Yvette Seppenwoolde, Hiroki Shirato, Kei Kitamura, Shinichi Shimizu, Marcel Van Herk, Joos V Lebesque, and Kazuo Miyasaka. Precise and real-time measurement of 3d tumor motion in lung due to breathing and heartbeat, measured during radiotherapy, 2002.
- [92] M. Seregini, C. Paganelli, J. Kipritidis, G. Baroni, and M. Riboldi. Pv-0282: Out-of-plane motion correction in orthogonal cine-mri registration. *Radiotherapy and Oncology*, 123:S147–S148, 5 2017.
- [93] Matteo Seregini, Chiara Paganelli, Paul Summers, Massimo Belomi, Guido Baroni, and Marco Riboldi. A hybrid image registration and matching framework for real-time motion tracking in mri-guided radiotherapy. *IEEE Transactions on Biomedical Engineering*, 65:131–139, 1 2018.
- [94] Mette K. Stam, Sjoerd P M Crijns, Bernard A. Zonnenberg, Maurits M. Barendrecht, Marco Van Vulpen, Jan J W Lagendijk, and Bas W. Raaymakers. Navigators for motion detection during real-time mri-guided radiotherapy. *Physics in Medicine and Biology*, 57:6797–6805, 11 2012.
- [95] Bjorn Stemkens, Rob H.N. Tijssen, Baudouin Denis De Senneville, Jan J.W. Lagendijk, and Cornelis A.T. Van Den Berg. Image-driven, model-based 3d abdominal motion estimation for mr-

- guided radiotherapy. *Physics in Medicine and Biology*, 61:5335–5355, 6 2016. Chaque phase du 4DMRI est recalée sur la phase 0. Les champs de def de toutes ces phases sont utilisés pour récupérer les 2 directions principales du mouvement avec une PCA. Ensuite ce modèle PCA est utilisé pour faire une reg 2D/ 3D MRI-MRI simplifiée et déformer la phase de référence. Je ne suis pas sur si c'est local ou global comme deformation, et la validation n'est pas très claire non plus.
- [96] Hope W. Stephen J. Korin, Farhad Farzaneh, Ronald C. Wright, and Riederer. Compensation for effects of linear motion in mr imaging. *Magnetic Resonance in Medicine*, 12:99–113, 1989.
- [97] Craig W Stevens, Reginald F Munden, Kenneth M Forster, Jason F Kelly, Zhongxing Liao, George Starkschall, Susan Tucker, and Ritsuko Komaki. Respiratory-driven lung tumor motion is independent of tumor size, tumor location, and pulmonary function, 2001.
- [98] Akulapalli Sudhakar. History of cancer, ancient and modern treatment methods. *Journal of Cancer Science Therapy*, 01:i–iv, 2009.
- [99] Saeid Asgari Taghanaki, Kumar Abhishek, Joseph Paul Cohen, Julien Cohen-Adad, and Ghassan Hamarneh. Deep semantic segmentation of natural and medical images: A review. 10 2019.
- [100] Seishin Takao, Naoki Miyamoto, Taeko Matsuura, Rikiya Onimaru, Norio Katoh, Tetsuya Inoue, Kenneth Lee Sutherland, Ryusuke Suzuki, Hiroki Shirato, and Shinichi Shimizu. Intrafractional baseline shift or drift of lung tumor motion during gated radiation therapy with a real-time tumor-tracking system. *International Journal of Radiation Oncology*Biology*Physics*, 94, 1 2016.
- [101] Scott Tyldesley, Geoff Delaney, Farshad Foroudi, Lisa Barbera, Marc Kerba, and William Mackillop. Estimating the need for radiotherapy for patients with prostate, breast, and lung cancers: Verification of model estimates of need with radiotherapy utilization data from british columbia. *International Journal of Radiation Oncology*Biology*Physics*, 79, 4 2011.

- [102] John R. van Sörnsen de Koste, Miguel A. Palacios, Anna M.E. Bruynzeel, Ben J. Slotman, Suresh Senan, and Frank J. Lagerwaard. Mr-guided gated stereotactic radiation therapy delivery for lung, adrenal, and pancreatic tumors: A geometric analysis. *International Journal of Radiation Oncology*Biology*Physics*, 102, 11 2018.
- [103] M VANHERK. Errors and margins in radiotherapy. *Seminars in Radiation Oncology*, 14, 1 2004.
- [104] Twyla Willoughby, Joerg Lehmann, José A. Bencomo, Shirish K. Jani, Lakshmi Santanam, Anil Sethi, Timothy D. Solberg, Wolfgang A. Tomé, and Timothy J. Waldron. Quality assurance for nonradiographic radiotherapy localization and positioning systems: Report of task group 147. *Medical Physics*, 39, 3 2012.
- [105] Jochem W.H. Wolthaus, Jan Jakob Sonke, Marcel van Herk, José S.A. Belderbos, Maddalena M.G. Rossi, Joos V. Lebesque, and Eugène M.F. Damen. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. *International Journal of Radiation Oncology Biology Physics*, 70:1229–1238, 3 2008.
- [106] Qing-San Xiang and Michael N Hoff. Banding artifact removal for bssfp imaging with an elliptical signal model. *Magnetic resonance in medicine*, 71(3):927–933, 2014.
- [107] S M Zenklusen, E Pedroni, and D Meer. A study on repainting strategies for treating moderately moving targets with proton pencil beam scanning at the new gantry 2 at psi. *Physics in Medicine and Biology*, 55, 9 2010.
- [108] Ye Zhang, A Knopf, C Tanner, and A J Lomax. Online image guided tumour tracking with scanned proton beams: a comprehensive simulation study. *Physics in Medicine and Biology*, 59, 12 2014.