

Design and implementation of a MRI compatible and dynamic phantom simulating the motion of a tumor in the liver under the breathing cycle

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Abstract

In the context of cancer treatment by proton therapy, research is carried out to use magnetic resonance imaging (MRI) to perform a real-time tracking of tumors during irradiation. The purpose of this combination is to avoid damaging the healthy tissue surrounding the tumor with the proton beam, while using a non-ionizing imaging method. Therefore, it is necessary to validate the tracking algorithms and real-time MRI sequences.

This master thesis is dedicated to the design and implementation of a dynamic MRI-compatible phantom simulating the motion of a tumor in a liver subjected to the breathing cycle. This phantom is a device representing a liver with hepatocellular carcinoma, a stomach and a pancreas, with a movement similar to the one induced by respiration, faithful to the anatomy and the magnetic properties of the human body. Many anatomical or mobile phantoms already exist, but the purpose here is to combine a reliable representation of the human body with the creation and the evaluation of a programmable movement in the same device.

The phantom, designed by following the Pahl and Beitz process, is composed of surrogate organs made of CAGN gels. These organs are placed in a box filled with water and attached to an elastic membrane. A programmable electropneumatic system creates a movement, similarly to a human diaphragm, by inflating and deflating the membrane.

The relaxation times of the synthetic organs belong to a range corresponding to the human organs values ($T1 = [458.7-1660]$ ms, $T2 = [39.3-89.1]$ ms). The displacement of the tumor is tracked in real time by a camera inside the MRI. The amplitude of the movement varies from 12.8 to 20.1 mm for a periodic and repeatable movement. Irregular breath patterns can be created with a maximum amplitude of 40 mm.

Résumé

Dans le cadre du traitement du cancer par proton thérapie, des recherches sont effectuées afin de faire de l'imagerie par résonance magnétique (IRM) en temps réel pour suivre le déplacement des tumeurs durant l'irradiation. Le but de cette combinaison est d'éviter d'endommager les tissus sains entourant la tumeur avec le faisceau de protons, tout en utilisant une méthode d'imagerie non ionisante. Il est donc nécessaire de valider les algorithmes de suivi et les séquences IRM temps réel.

Ce mémoire est dédié à la conception et à la réalisation d'un fantôme IRM dynamique simulant le mouvement d'une tumeur dans un foie soumis au cycle respiratoire. Ce fantôme est un dispositif représentant un foie avec un carcinome hépatocellulaire, un estomac et un pancréas, ayant un mouvement semblable à celui créé par la respiration, fidèles à l'anatomie et aux propriétés magnétiques du corps humain. Il existe déjà de nombreux fantômes anatomiques ou mobiles, mais celui-ci a pour but de combiner la représentation fiable du corps humain avec la possibilité de créer un mouvement programmable et de l'évaluer dans un même dispositif.

Le fantôme, conçu en suivant la démarche de Pahl et Beitz, est composé d'organes synthétiques faits en gels CAGN. Ces organes sont placés dans une boîte remplie d'eau et attachés à une membrane élastique. Un système électropneumatique programmable permet de créer un mouvement, semblable à celui d'un diaphragme humain, en gonflant et dégonflant la membrane.

Les temps de relaxations des organes synthétiques appartiennent à un intervalle de valeurs correspondant à celui des organes humains ($T1=[458.7-1660]$ ms, $T2=[39.3-89.1]$ ms). Le déplacement de la tumeur est suivi en temps réel par une caméra à l'intérieur de l'IRM. L'amplitude du mouvement varie de 12.8 à 20.1 mm pour un mouvement périodique et répétable. Des modèles de respirations irrégulières peuvent être créés avec une amplitude maximale de 40 mm.

Contents

1	Introduction	1
1	Objectives of our research	2
2	Structure	2
2	Background	3
1	Cancer statistics	3
2	Cancer and treatment possibilities	5
2.1	IBA - the world leader in proton therapy (PT)	8
2.2	ImagX.R - Implementing Medical Imaging Solutions	9
3	Cancer and diagnostic possibilities	9
4	Magnetic resonance imaging (MRI)	11
4.1	The physics of MRI	11
4.2	Image reconstruction from the magnetic resonance signal	17
4.3	Artifacts	23
3	Design of the solution	26
1	Innovation Classes	27
2	Needs and requirements	28
3	State of the art of MRI phantoms	29
3.1	Commercialized phantoms	30
3.2	Experimental phantoms	32
4	Pahl and Beitz design process	34
4.1	Functional analysis	35
4.2	Search for solutions	37
4.3	Choosing the solution	37
4.4	Final Solution	39
4	Technical characteristics	41
1	The box	42
2	The membrane	43
3	Electro-pneumatic system	44
4	Tissue surrogates	48
5	Molds of the organs	56
6	Connecting the organs together and to the membrane	57
7	Visual tracking	58
5	Results and discussion	60
1	Motion test	61
1.1	Similarity with the real human motion	63
1.2	Repeatability and reproducibility of the motion	64
2	Tissue surrogates	69
2.1	Organ-like gels	70

2.2	Test samples	74
3	Achieved objectives	78
4	Discussion	79
4.1	Design of the motion mechanism	79
4.2	Membrane deformation	80
4.3	Visual tracking	80
4.4	Tissue surrogates	80
6	Conclusion	82
A	Nuclear Magnetic Resonance	89
B	Needs and requirements	91
C	Morphological Graph	94
D	Blueprints of the box	96
E	Technical sheets of the tissue surrogates	98
F	Real-time tracking	102
G	Gel Samples	104

Abbreviations and symbols

α	: Flip angle
γ	: $2\pi\Upsilon$
ΔB_0	: Spread of the external field
μ	: Magnetic moment
Υ	: Gyromagnetic ratio
χ	: Magnetic susceptibility
$\mathbf{B}_0$	: Main (or external) induction magnetic field inside the MRI
B_0	: Intensity of $\mathbf{B}_0$
$\mathbf{B}_1(\mathbf{t})$	: Excitation RF-pulse
$\mathbf{C}$	: Magnetic torque
CHR	: Centre Hospitalier Régional (Regional Hospital Center)
CIRS	: Computerized Imaging Reference Systems
CT	: Computered Tomography
CTV	: Clinical Target Volume
CUSL	: Cliniques Universitaires Saint-Luc, UCL, Bruxelles
DICOM	: Digital Imaging and COMmunications in medicine
f_0	: Larmor frequency
FDA	: US Food and Drug Administration
FID	: Free Induction Decay
GTV	: Gross Tumour Volume
G_x, G_y, G_z	: Gradient field in the X, Y and Z axis
H	: Induction magnetic field
HCC	: Hepatocellular carcinoma
I	: Spin number
$\mathbf{I}_x, \mathbf{I}_y, \mathbf{I}_z$	: Unit vectors in the X, Y and Z axis
IARC	: International Agency for Research on Cancer
IBA	: Ion Beam Application : IBA SA, Louvain-la-Neuve, Belgique
INRC	: Italian National Research Council
IGRT	: Image-Guided RadioTherapy
LINAC	: LiNear ACcelerator
M	: Macroscopic magnetization
M_z	: Longitudinal component of $\mathbf{M}$
M_{xy}	: Transverse component of $\mathbf{M}$
M.D.	: Medical Doctor
MF	: Main Function
MR-LINAC	: Magnetic Resonance guided LiNear ACcelerator
MRI	: Magnetic Resonance Imaging
MRI-GPT	: Magnetic Resonance Image-Guided Proton Therapy
NaCl	: Sodium Chloride
NEX	: Number of EXcitations (average)

NCI	: National Cancer Institute
NMR	: Nuclear Magnetic Resonance
PET	: Positron Emission Tomography
PF	: Principal Function
PD	: Proton Density
PT	: Proton Therapy
PTV	: Planning Target Volume
RF	: Radio Frequency
ROI	: Region Of Interest
RT	: Radiation Therapy
SAR	: Specific Absorption Rate
SI	: Specific Ionization
SNR	: Signal-to-Noise Ratio
T_1	: Characteristic time of the longitudinal relaxation
T_2	: Characteristic time of the transverse relaxation
T_2^*	: Effective relaxation time for the transverse recovery
T_{acq}	: Acquisition time for one image
T_{RF}	: Emission time
TE	: Echo delay
TF	: Technical Function
TI	: Inversion time
TR	: Repetition delay
UCL	: Université Catholique de Louvain
V	: Volume

Chapter 1

Introduction

In the context of the fight against cancer, proton therapy is a cutting-edge technology that has been developed during the past decades and is still evolving. Among the future objectives, the research tries to combine the proton treatment with magnetic resonance imaging (MRI) in order to achieve the real-time tracking of the tumor while irradiating it. Therefore, the purpose of this master thesis is to design and implement a testing device, located inside the MRI scanner, to assess the ability of the system to track a tumor in real time.

Two main reasons support the choice of combining proton therapy with magnetic resonance rather than with another medical imaging modality. First, MRI has the unrivaled ability to distinguish soft tissues, where a lot of tumors are located. Secondly, MRI is non-ionizing, which is essential for real-time tracking. So far, CT scans (X-ray) are still frequently used to localize the tumors at rest. The amount of radiations sent to the patient is considered acceptable compared to the dose delivered during the treatment. Yet, for real-time tracking, the exposure strongly increases and could be damaging for the patient.

Despite these advantages, MRI also has some limitations. The magnetic field used by the system induces distortions in the path of the proton beam. Though they can be computed [1], it increases the complexity of the method. Moreover, all the magnetizable materials and sensitive magnetic parts have to be shielded with a Faraday cage to avoid affecting the quality of the images. Finally, some geometric distortions of the anatomy are caused by the MRI acquisition. However, they are generally corrected during the post processing of the signal with an error margin smaller than one millimeter [2], which is the required precision for proton therapy.

The hybrid MRI-proton therapy systems could lead to a real increase in the performance of the treatment, as the MR-LINAC system did with radiotherapy [3]. However, the benefits of proton therapy are greater compared to radiotherapy thanks to the sharp dose delivery to the target. Today, the treatment planning is based on a static image where three regions are selected. As explained by Burnet et al. :

"There are three main volumes in radiotherapy planning. The first is the position and extent of gross tumour, i.e. what can be seen, palpated or imaged; this is known as the gross tumour volume (GTV). (...) The second volume contains the GTV, plus a margin for sub-clinical disease spread which therefore cannot be fully imaged; this is known as the clinical target volume (CTV). The CTV is important because this volume must be adequately treated to achieve cure. The third volume, the planning target volume (PTV), allows for uncertainties in planning or treatment delivery. It is a geometric concept designed to ensure that the radiotherapy dose is actually delivered to the CTV." [4]

The main purpose of the real-time tracking is to minimize as much as possible the incertitude on the position of the tumor, such that the size of the PTV can be reduced. The CTV could be

extracted from the real-time images and adapted over time while the tumor is moving. Instead of aiming at a large area in which the tumor moves, the proton beam would follow the displacement of the target and avoid healthy tissues surrounding it and, therefore, reducing the side effects of the treatment.

1 Objectives of our research

The potential of a real-time tracking of a tumor located in a soft tissue is undoubtedly enormous. However, the acquisition parameters during mobile imaging have to be tuned and the tumor identification softwares still have to be developed. This is the goal of the PhD thesis of Damien Dasnoy-Sumell. To help him assess the relevance of the achievements in this field of research, our master thesis was to design and implement a calibration device. In medical terms, this calibration system is called a "phantom" : *"a device or object used in several imaging processes to visualize or improve visualization by simulating the conditions encountered in different procedures"* [5]. Our phantom, which focuses on liver tumors, will be fully described in this report. Although some anatomical or mobile phantoms already exist (see Chapter 3, Section 3), our device aims to combine these two aspects with an external real-time tracking of the displacements of the tumor.

To do this, a tumor-like object has to be placed in an environment similar to a human liver and its surrounding tissues, during a motion cycle resembling the breathing cycle of a human being. The main goal is to validate MRI-tracking methods that should detect the contour of the tumor with a millimetric precision despite movements induced by the inner functioning of the human body. To allow the recursive usage, the exact dimensions and displacements in the phantom have to be handled properly. Moreover, the materials used have to respect the constraints imposed by MRI environments and must be representative of the human structure.

Once validated, the tracking method applied on the phantom with well-known characteristics should be ultimately used *in vivo* for cancer treatment planning and treatment guidance.

2 Structure

In addition to this introduction, the next chapter highlights the incentives and the background embracing the development of the phantom. Considering the particular environment created for MRI, a section is dedicated to the understanding of this imaging modality.

The third chapter is devoted to the description of the design process, i.e. the step defining a suitable solution in regards to the needs and requirements applicable to the phantom. The state of the art concerning MRI compatible phantoms is drawn in parallel with the formulation of the solution.

After describing the conceptual solution in Chapter 3, the technical aspects of the implemented solution are detailed in Chapter 4. The various components of the phantom, such the materials that compose it or the circuits that supply it, are analyzed in turn.

In Chapter 5, the produced device is evaluated through a series of tests and the results of the latter are explained. Particular interest is given to the description of the motion patterns the phantom follows and its magnetic properties. The requirements concerning the device are confronted to the achievements at this point.

At the end of this master thesis, several conclusions can be stated on the design of dynamic phantoms for the calibration and validation of MR image acquisition process. The last chapter addresses our accomplishments in this direction.

Chapter 2

Background

This chapter is addressed to the reader who wishes to grasp basic knowledge over cancer from general information statistics to treatment possibilities. The scope of this chapter also extends to a technical explanation of how MRI works. As being at the heart of the development of proton therapy, the company Ion Beam Application (IBA) and their partnership with the Université Catholique de Louvain (UCL) on the collaborative project ImagX.R will be introduced as well.

1 Cancer statistics

Under the urge of fighting the ever-growing burden of cancer, the World Health Organization has created the International Agency for Research on Cancer (IARC) in 1965. This agency strives to prevent cancer worldwide and collects essential data related to this disorder from regions all over the world. In 2012, the latest official update of the IARC's global database, a total estimation of 14,1 millions of cancer diagnosis was reported over the year. The pie chart on Figure 2.1 displays the distribution of the most common cancer sites, representing 65% of the cases that year. All of them are soft tissue cancers. The IARC denotes that the overall age-standardized cancer incidence rate is almost 25% higher in men than in women. On top of its high rate of incidence, cancer is, regrettably, one of the leading causes of death worldwide. In 2012, the estimated amount of cancer deaths reached 8.2 millions. This represents 14.5% of the global deaths [6].

The bar chart on Figure 2.2 illustrates the ratio between incidence and mortality in six of the most common types of cancer diagnosed around the world. Lung cancer is by far the most frequent and is responsible of most of the deaths related to cancer. However, liver cancers have an extremely high level of mortality compared to the others. With an overall ratio of mortality to incidence of 0.95 according to the IARC, liver cancers are particularly pernicious. Hepatic cancers affect especially the male population (70% of the diagnosed cases in 2012) and the less developed regions of the world (83% of the cases in 2012, 50% in China alone) as suggested on Figure 2.3. Moreover, mostly men aged 65 and older develop liver cancer, i.e. over 70% of the diagnosed cases [7]. It is interesting to note that, though liver cancer incidence has different rates according to the status of the regions (highly- or less-developed regions), the overall ratio of mortality to incidence is currently the same across the world, independently from the level of development of the regions.

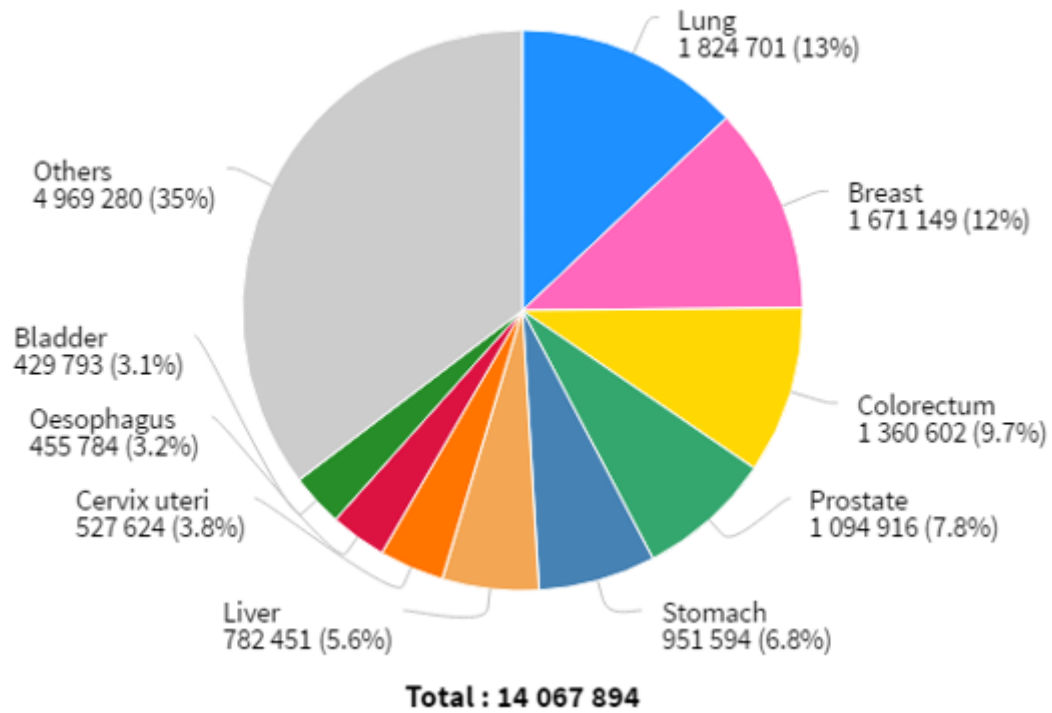


Figure 2.1: Estimated number of incident cancer cases, both sexes, worldwide in 2012 [6]

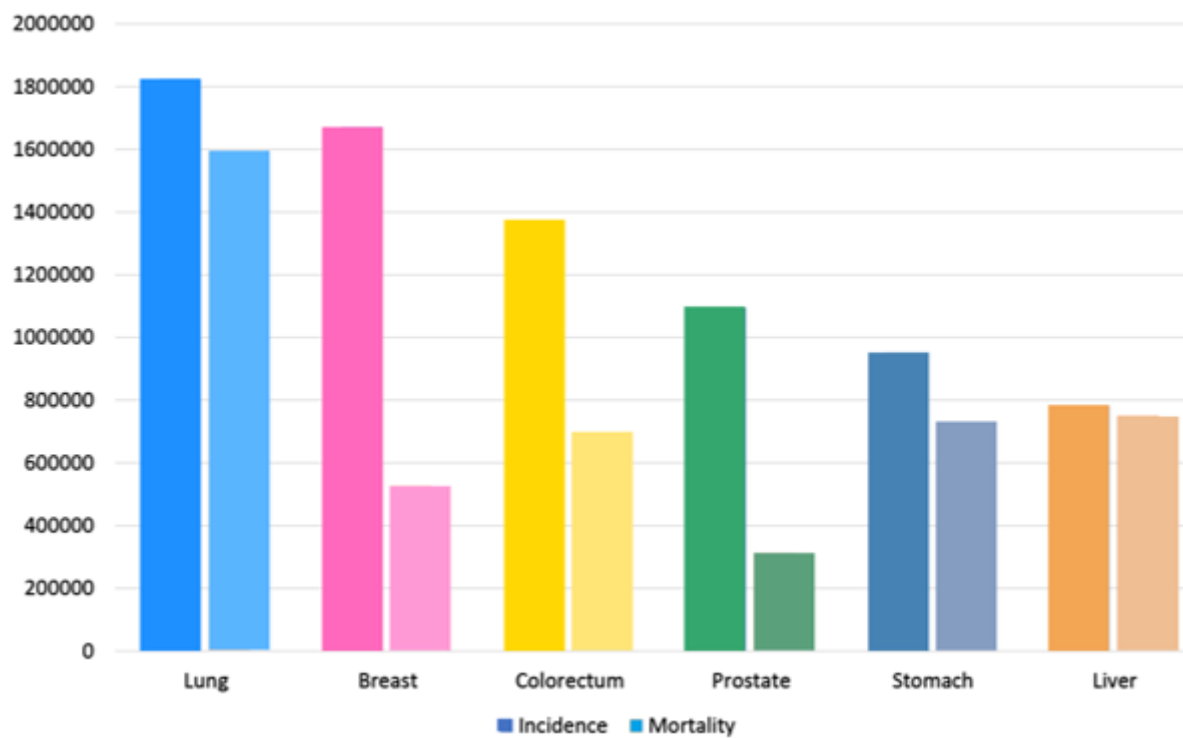


Figure 2.2: Estimated incident versus mortality cases, both sexes, worldwide in 2012 [6]

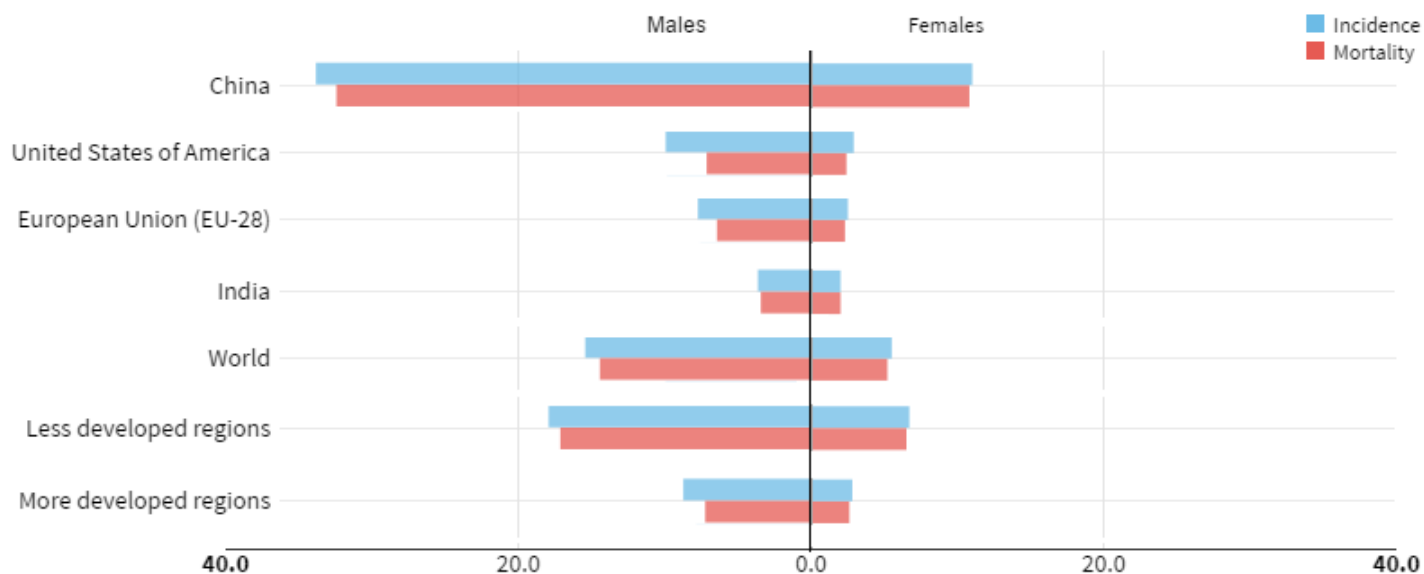


Figure 2.3: Estimated aged-standardized rates (liver cancer), worldwide in 2012 (per 100.000) [6]

Since 2012, the global cancer incidence rate has kept growing at a dramatic pace. The IARC predicts a rise of cancer diagnosis to 20 millions per year by 2025, with an increase of 70% of the cases in the low and middle-income countries [8]. Sadly, the mortality rate of cancers will also expand in the following years. The National Cancer Institute (NCI) of the U.S Department of Health and Human Services adds to IARC's statistics an increase of 60% of the cancer fatalities by 2030, reaching a total amount of 13.1 millions per year worldwide [9].

According to the NCI, the growing number of cancer incidence is essentially correlated to the aging population since cancer rates increase with age. Pollution, behavioral and dietary risks such as tobacco smoking, obesity and excessive alcohol intake also have a major impact on this rising tendency [9]. To halt the corresponding mortality increase, in particular for soft tissue cancers such as liver cancer, prevention and improvement of the existing treatments are critical.

2 Cancer and treatment possibilities¹

Cancer is the term used to design a collection of related disorders. In all cases, the disease is provoked by an uncontrollable multiplication of cells, which spread into the surrounding tissues. The abnormal cell proliferation has a genetic origin. Genes are responsible of the way cells function and develop. The deterioration of the DNA sections coding the genes, called a mutation, alters the growth and division instructions as well as the DNA repair functions. These genetic modifications can be inherited from the parents. Their incidence may also be a result of errors during the division process of healthy cells. Furthermore, cancers can be induced by exposure to carcinogenic environments such as the ultraviolet rays of the sun or excessive alcohol consumption.

The development of the cancer leads to the formation of solid tumors in most of the cases. Tumors are masses of tissue and may be characterized as malignant or benign depending on how they affect their surroundings. Cancerous tumors are malignant. This means that they invade the neighbouring tissues and disrupt their normal functioning. Some cancer cells may even attack

¹The introductive part of this section is greatly inspired by the excellent content of the National Cancer Institute's (NCI) website [10]

other regions of the body by breaking off the tumor and travelling through the blood and the lymph system. Moreover, there is a risk that the malignant tumor regenerates if its resection is not properly done. On the other hand, benign tumors do not spread out of the boundaries of their own tissue formation and do not grow back after removal. However, they may affect the health of the patient by compressing vital organs as they expand.

The composition of the tumor may vary from one type of cancer to another. Cancers are usually categorized according to the organ or tissue from which they grow. At least a hundred of cancers have been listed. The tumors also have their own specific classification based on the types of cells that compose them. The most common tumors are carcinomas; a collection of degenerated epithelial cells, which are the cells that cover the inside and the outside surfaces of the body. They occur in soft tissues. Another common type of cancer is sarcoma which can begin in bone and soft tissues.

Nowadays, three treatments are mostly used, and often combined, to eradicate or at least to contain tumors:

- Physicians may proceed to a **surgery** consisting in removing the tumor from the patient's body. The operation necessitates anesthesia and is usually heavy to recover from. The surgeon has different intervention means such as scalpels, laser beams or even extremely cold substances for cryosurgery.
- Another type of cancer treatment is **chemotherapy**. The physician provides drugs to the patient to reduce the swelling of the tumor by affecting the cell growth mechanism. In most of the cases, chemotherapy is combined with another cancer treatment either to reduce the size of the tumor beforehand or to eliminate any harmful remains afterwards. Chemotherapy has impressive side effects since it also attacks healthy cells. As for surgery, chemotherapy is invasive.
- The third most common possibility of treatment is **radiotherapy**. This technique takes advantage of the energy transported by ionizing radiations or charged particles projected, in a concentrated beam, onto the cancerous cells to destroy them. If sufficiently high, the amount of energy delivered to the cell is able to break the cell's genome in parts. In that case, the death of any stroked cell is inevitable. Thus it is of prime importance to target the tumor exactly and to avoid hitting any surrounding tissues with the highly-energetic beam.

Since cancer treatment is demanding for the patient, it is usually scheduled over several sessions. Their frequency of application depends on the type of treatment prescribed and the recommended operating mode in addition to the data of the patient. This latter may undergo daily treatments for a week to weekly treatments with several weeks of rest between each session [11][12]. In radiation therapy, it is particularly important to space the dose delivery in time. The total amount of prescribed radiation is divided into various fractions to enable healthy tissues to recover between sessions. Indeed, healthy tissues are affected during the ionization of the tumor and their exposure to radiations has to be minimized. In addition to the splitting of the dose, each fraction is distributed in the form of several rays shot from different angles as depicted on Figure 2.4. This way, maximal dose is delivered at the intersection of the rays while the surroundings are less irradiated. The sum of all the fractions adds up to reach the total dose necessary to resection the tumor. However, in order to compensate the imprecision in the localization of the tumor during the treatment, security margins enclosing the tumor are introduced in the treatment plan [4]. They have a significant impact on the dose delivery to the surrounding tissues [13].

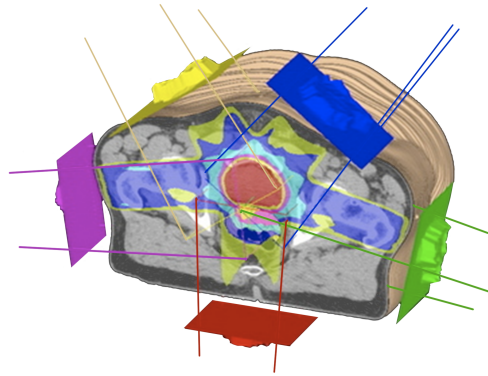


Figure 2.4: Prostate treatment plan illustrating the distribution of the radiation around the target (in red, at the center of the image) [14]

In the context of our master thesis, particular interest is given to proton therapy, which is a cutting-edge radiotherapy technology. Unlike conventional radiation therapy that bombards tumors with x-rays, proton therapy uses positively charged particles, called ions, to eradicate cancerous cells. Heavy charged particles have the potential to enable a much more localized ionizing dose delivery than photon irradiation. Indeed, an energetic charged particle leaves a track of ionized atoms and ejected electrons in its path after passing through matter. This amount of ion pairs produced per unit length of the path is called the specific ionization (SI). It decreases with the velocity of the charged particle (shorter time nearby the atom) and increases with the electrical charge (increased attraction of opposite charges). As the particle slows down, the SI reaches a maximum (the Bragg peak - in blue on Fig. 2.5) and then decreases sharply once the particle has lost its kinetic energy and is neutralized [15].

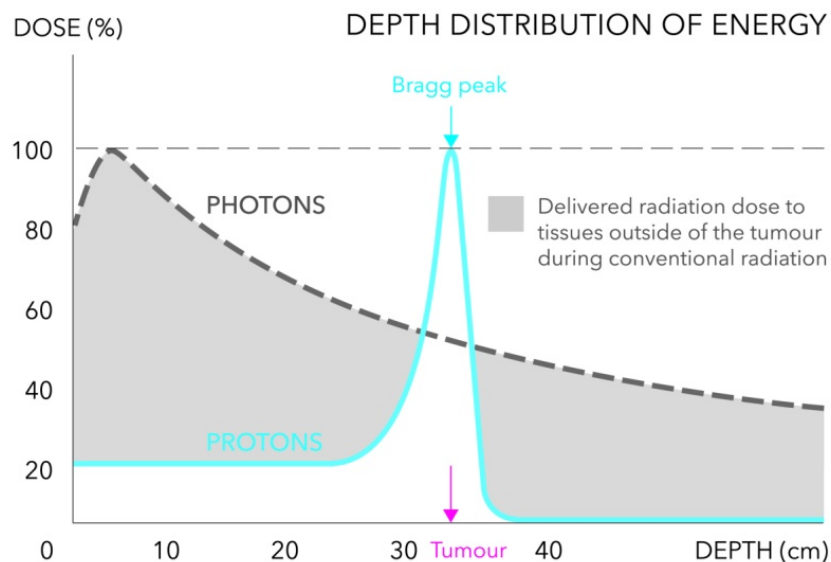


Figure 2.5: Radiation dose delivery to the patient in conventional radiotherapy (grey) and in proton therapy (blue) [16]

The particles mainly used in ion radiation are hydrogen atomic nuclei (protons) and carbon atomic nuclei, which are very "heavy". Figure 2.6 illustrates their journey from one end of an ion therapy system to the other end where the patient lies. Atomic nuclei are, first, accelerated in a cyclotron (synchrotron for carbon nuclei) to about one third of the speed of light. Then, the high-speed particles are conducted to the nozzle of the therapy device in a highly concentrated beam by a set of directional magnets. From there, the protons are shot with a sub-millimetric

precision. The depth of penetration of the beam depends on the speed of the ions and of the composition of the medium they travel through.

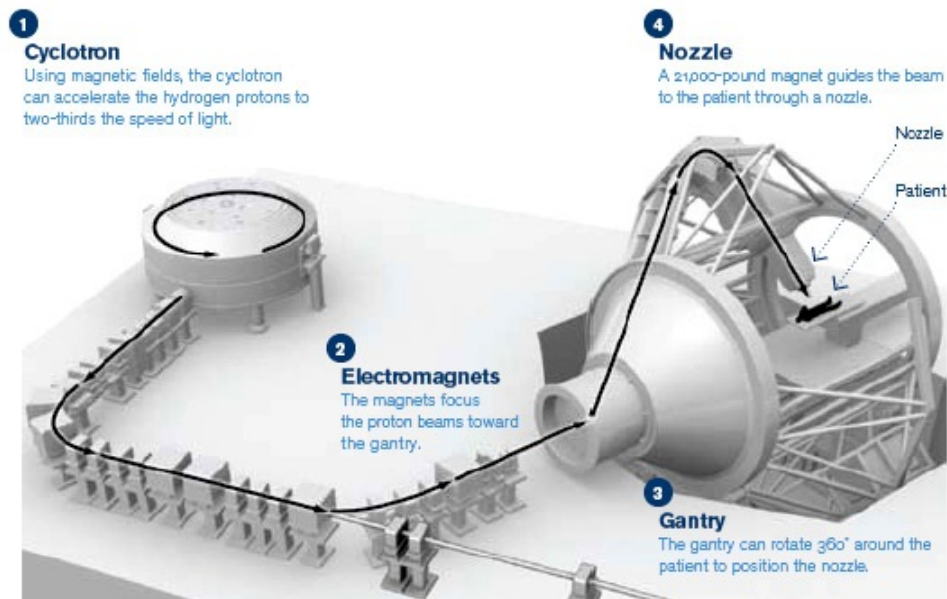


Figure 2.6: Illustration of a proton therapy system [17]

2.1 IBA - the world leader in proton therapy (PT)

The company Ion Beam Application (IBA), the world leader in proton therapy (PT), is looking forward to combining the outstanding efficiency of PT with the high contrast resolution of MRI in real-time acquisition in order to provide image-guided radiotherapy (IGRT).

The company has installed over 50 proton therapy centers worldwide and has reached the symbolic threshold of 50 000 patients treated in 2017 [18]. IBA has developed innovative solutions to overcome challenges related to PT, such as *Proteus®One*, which cleverly answers the size issue of the infrastructures required for PT [19]. IBA is now facing another bottleneck in regards of their expansion as PT leaders : the ability of knowing the exact position of the tumor at all time during the treatment.

In principle, the Bragg peak can be exploited to apply an unmatched precision for dose delivery to the target since little energy is lost before the peak and no energy remains after it [20] [21]. The contrast between dose distribution in conventional RT and PT can be appreciated on Figure 2.5. However, with current technologies, only a few tumors, essentially located in the brain, the head and the neck, can truly benefit from PT's sharp dose deposition. Because of its high precision, proton therapy is extremely sensitive to mispositioning, even by a few millimeters.

As stated by J. Hartman et al. from the Universitaire Medisch Centrum Utrecht [20], in conventional RT, such a small error would result in a few percentage dose change while it could lead to a 100% dose change in proton therapy as suggested on Figure 2.5. Indeed, while it is only necessary to aim in the correct direction with a precise beam in photon irradiation, with proton therapy, the exact point where the beam will stop requires additional predictions. Depth information of the tumor is critical for the use of PT onto patient.

Moreover, soft tissue tumors are more difficult to accurately locate because they are subject to motion. Since, radiotherapy and proton therapy treatments are divided over several sessions, the organs may move or be filled differently during the time elapsed between two fraction deliveries. In addition to these variations, organs of the abdominal and thoracic regions follow the motion essentially induced by the breathing and the heart beat. All these changes may lead to a mispositioning of the target intra- and inter-fraction².

One approach to reduce the effect of motion during treatment is to make the proton therapy dose distribution more robust to anatomical motion. Related to the range uncertainty, margins are added to the target volume. This partly spoils the benefits of the Bragg peak [20]. Furthermore, cutting-edge photon therapy devices have already integrated state of the art imaging systems such as cone beam CT guided radiotherapy systems or MR-Linac to allow consequential margin reductions. Such target volume reduction outperforms the integral dose reduction due to current Bragg peak applications [20][22]. Thus the key to overcome anatomical motion in proton therapy is to integrate **real-time image guidance** as well. The combination between MRI real-time images and the Bragg peak can be used for high precision stereotactic irradiation for moving targets, as suggested by Hartman et al. [20].

Nowadays, only 1% of the cancers are treated by proton therapy. The literature agrees that 20% of the actual cases should benefit from this impressive technology [18] and this rate could explode with the commercialization of hybrid MRI-PT systems.

2.2 ImagX.R - Implementing Medical Imaging Solutions

IBA and the Université Catholique de Louvain (UCL) have joined their intellectual, equipmental and funding capacities to create ImagX.R. - previously named ImagX -, a team of searchers involved in the applications of medical imaging to proton therapy. Their aim is to develop advanced solutions for ensuring the reduction of range uncertainties and the treatment of mobile tumors [23].

As part of the team, Damien Dasnoy-Sumell is achieving a PhD thesis consisting in the tracking of soft tissue tumors under internal induced motion, notably due to the respiratory cycle. The objective of this research is to optimize the dose delivery to the tumor despite disturbance in the image flow. In consequence, the duration of the treatment could be reduced, the evolution of the tumor could be better supervised all along the treatment sessions and the costs of the treatment could decrease ultimately. In order to ensure fast acquisition times needed in the case of image guidance, Damien Dasnoy-Sumell studies the implementation of balanced steady-state sequences in the image acquisition process. To validate the use of such a sequence and its accuracy in real-time monitoring, the phantom designed in the context of this master thesis will be used.

3 Cancer and diagnostic possibilities

In addition to treatment possibilities, cancer diagnosis and cancer follow-up technologies have been developed since the discovery of x-rays by W. C. Röntgen in 1895 [24]. This field of research and its applications are entitled medical imaging as it gives the opportunity to practitioners to visualize anatomical and physiological data on imaging devices. The physics of medical imaging is mainly governed by wave characteristics and signal processing. Current technologies are able to distinguish healthy tissues from cancerous tissues and other disorders thanks to the abnormal composition and the unusual behaviors of the affected tissues.

²Intra : during the same treatment session; Inter : between two treatment sessions

The major imaging modalities in use in the medical field are the following [15][25]:

- **X-ray projection imaging** is the first technology that enabled to see through the human body. X-rays, which are ionizing electromagnetic waves, are projected onto a patient on one side and a screen collects the transmitted radiations on the other side of the examined body. The resulting images are 2D projections of the 3D anatomy so thickness information is lost. The spatial resolution is very good but the technique has a poor temporal resolution. One may note that no computer is necessary to acquire an image in this case. However, the digitalization of the technique has enabled to accelerate the image acquisition and to visualize live moving images with fluoroscopic cameras.
- In **computered tomography (CT)**, x-rays are also used to explore the human anatomy. Yet, the actual processes are entirely digitalized and the imaged model is acquired slice by slice such that depth information is re-established. The produced 3D models and slice images display great contrasts and spatial resolution at very fast rates thanks to multi-layer CTs and cone beam CTs. However, exposure to ionizing radiations is dangerous for health.
- **Magnetic resonance imaging** takes advantage from the massive presence of hydrogen in the human body and from the nuclear magnetic resonance principle (see Appendix A). When exposed to varying magnetic signals in intense magnetic fields, protons (hydrogen nucleons) emit radio frequency signals, which are collected by antennae and processed by computers. Actual computing devices and image reconstruction algorithms are capable of acquiring 3D models at very fast rates. The images display high and adjustable contrasts, which is very useful for soft tissue examination.
- **Ultrasonic imaging** uses acoustic waves of very high frequencies to interact with the tissues of the human body. The echoes of these waves inform on the anatomy and also on the motion of the tissue they reach. The acquired response is almost instantaneous. However, this technique is very noise-sensitive and the device has to be applied as close as possible to the patient to be efficient.
- **Nuclear Imaging**, and particularly **PET scan**, captures the signals resulting from the annihilation of positrons. When the photons, i.e. energy bundles travelling through space, are absorbed by a nucleus, a pair of electron-positron is created. Then, the positron fades quickly into two new photons, which are ejected in opposite directions. After travelling through matter in a relatively straight path, these photons are captured by detectors moved all around the examined section and their spatial information is recovered. This technique enables the construction of maps of the activity in the human tissues. However, the precise localization of this activity is still limited ($> mm$).

According to M.D. Alexandre Mosseray, the head of the medical imaging department of the CHR Namur, three aspects are essential in cancer imaging : health of the patient, quality of the images and reproducibility of the images.

- The *patient's health* is impaired by repetitive exposition to radiative waves. In the context of real-time imaging during a treatment-long length of time, the dose delivered by ionizing imaging modalities such as CT scans or fluoroscopy may become critical for the patient. Therefore, strong interest is shown for non-ionizing imaging systems such as MRI for this type of application.
- The *quality of the image* is related to the spatial and temporal resolution, the contrasts between the different materials and the noise affecting the signal. The imaging modality which optimizes these features for a given application will usually be preferred. In cancer

imaging, MRI is mostly used for local examinations of soft tissues while PET scans are better suited for global views. CT scans are also often proceeded because of their unrivalled capability to outline the geometries of the human anatomy.

- *Reproducibility* is important for the follow-up of tumors between treatment sessions, which may be spaced of several weeks as stated in the previous section. MRI is limited by the high variability in the measurements, essentially related to the subjectivity of the interpretation of the MR image [26]. Automation and calibration of the imaging process is therefore primordial to overcome this limitation [27].

Consequently, MRI is a valuable imaging modality for its unrivalled ability to outline soft tissues and since it is non ionizing. These two characteristics make MRI a choice of the first order for applications in continuous imaging during cancer treatment. Shortcomings concerning the reproducibility of the images, the rapidity of the reconstruction of the image and the quality of the image are essentially related to technological challenges.

4 Magnetic resonance imaging (MRI)³

A good understanding of the physics of MRI is essential for the improvement of this technology. Besides, in our case, understanding the MRI was fundamental for the design of the phantom explained further in this document. This section introduces the basic notions of the MRI technology. The Figure 2.7⁴ shows a drawing of the MRI device to give a first idea of what it looks like.

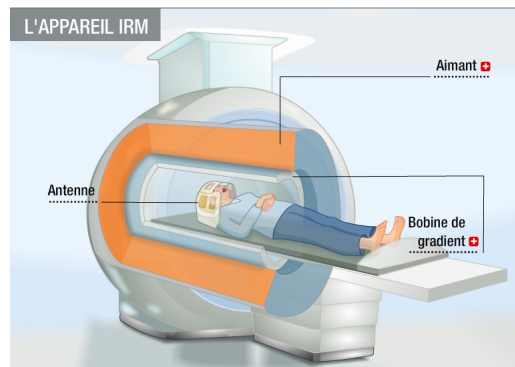


Figure 2.7: Drawing of an MRI scanner with a patient inside [28]

The first part of this section is dedicated to the explanation and description of the exploitation of the nuclear magnetic resonance (NMR) phenomenon for medical imaging, staying in the macroscopic world of traditional physics. For further information over the quantum explanation of NMR, the reader is invited to take a look at Appendix A. The second part covers the image reconstruction from a magnetic resonance signal and the instrumentation used. The last part of this section will detail the most common artifacts and their origins.

4.1 The physics of MRI

Images from the inside of the human being are obtained by processing the waves that interact with the inspected body. In MRI, electromagnetic waves in the radiofrequency spectrum trigger the nuclear magnetic resonance phenomenon of hydrogen nuclei to probe into the depths of the human body. This phenomenon is governed by the laws of the quantum world. However,

³This chapter is based on the chapter 4 of the lecture *GBIO2050 Imagerie médicale* of F. Peeters [25]

⁴Translation of the indications : antenne = antenna, aimant = magnet, bobine de gradient = gradient coil

traditional physics can explain the phenomenon at the macroscopic level, thanks to the statistical laws of Boltzmann. Appendix A introduces the quantum quantities used in the following sections; in particular, the explanation of the spins and of the Larmor frequency.

Magnetization

The key concept that links the quantum world to the macroscopic one is the macroscopic magnetization, which is the vectorial sum of the magnetic moments of the spins in a given volume :

$$\mathbf{M} = \frac{1}{V} \sum_i \mu_i \quad (2.1)$$

The statistical formulae of Boltzmann give the ratio between parallel and antiparallel spins in a magnetic field. They estimate that the number of parallel spins is larger than the number of antiparallel spins and the gap between the two populations is proportional to the intensity of the field $\mathbf{B}_0$ (see Figure 2.8). Hence, the longitudinal component of $\mathbf{M}$ is not null. However, the spins are not in phase so the transverse component of $\mathbf{M}$ is canceled out.

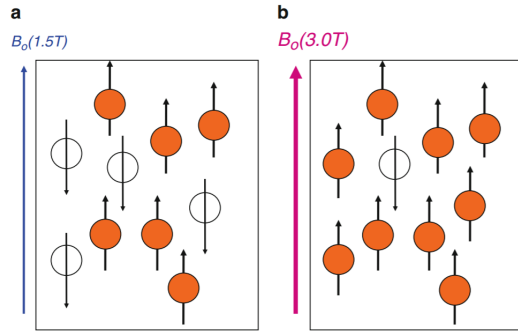


Figure 2.8: Influence of the field intensity on the spin orientation and the equilibrium magnetization [29].

The equilibrium magnetization is then :

$$\mathbf{M}_0 = \beta B_0 \mathbf{I}_z, \quad (2.2)$$

with β a factor which depends, among others, on the Larmor frequency, the spin density and the local temperature.

Magnetic resonance

To recover the image of the inspected body part, the response of the medium to a change in the magnetic field is measured. To do so, the spin system is excited by a RF-pulse, which interacts with the nuclei and creates a transverse component of $\mathbf{M}$. This pulse $\mathbf{B}_1(\mathbf{t})$ oscillates in resonance at the Larmor frequency of the hydrogen nuclei :

$$\mathbf{B}_1(\mathbf{t}) = 2B_1(t) \cos(2\pi f_0 t + \varphi) \mathbf{I}_{xy} \quad (2.3)$$

Excitation

To simplify the explanation and representations of the problem, we will consider a rotating frame (X' , Y' , $Z'=Z$) at the angular speed $\omega_0 = 2\pi f_0$. When the only existing field is $\mathbf{B}_0$, the vector $\mathbf{M}$ is aligned with the Z axis. Once the RF-pulse is emitted, the spins begin to precess around this new field. In the rotating frame, it will be seen as a rotation of $\mathbf{M}$ at the speed $\omega_1 = \gamma B_1$. In the fixed frame, this motion creates a kind of spiral shape. The evolution of the vector $\mathbf{M}$ during the excitation phase in the two frames is illustrated in the Figure 2.9.

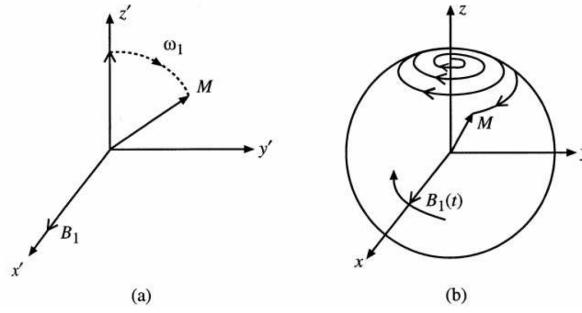


Figure 2.9: Evolution of the macroscopic magnetization vector during the excitation phase in the rotating frame (a) and in the fixed frame (b). [25]

For a finite emission time T_{RF} of the RF-pulse, the $\mathbf{M}$ vector will be tilted over an angle α , the **flip angle**, given by :

$$\alpha = \gamma \int_{T_{RF}} B_1(t) dt \quad (2.4)$$

If the emission time is designed such that $\alpha = 90^\circ$, the pulse is called a 90° -pulse and there is no longitudinal component anymore. In general, the magnetization can be expressed as :

$$\mathbf{M} = M_z \mathbf{I}_z + M_{xy} \mathbf{I}_{xy} \quad (2.5)$$

with M_z the longitudinal component and M_{xy} the transverse component of the magnetization.

Relaxation

After the excitation, the system will come back to its equilibrium state by two simultaneous and independent relaxations of the magnetization. The specific rates at which the magnetization recovers the equilibrium are essential for the image contrast and are characteristic to each material being observed.

The first relaxation is the one of the longitudinal component of the magnetization, also called spin-lattice recovery or **T_1 relaxation**. It corresponds to the gradual decay of the magnetic moment to align itself with the Z axis of the principal magnetic field $\mathbf{B}_0$. Figure 2.10 shows this phenomenon. The decline of M_z is a decreasing exponential of the shape :

$$M_z(t) = M_0 + (M_z(0) - M_0) \exp\left(\frac{-t}{T_1}\right) \quad (2.6)$$

with $M_z(0)$ the amplitude of M_z just after the excitation.

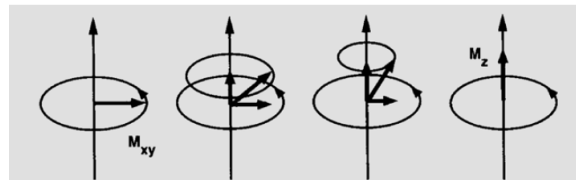


Figure 2.10: Illustration of the longitudinal relaxation after the excitation phase with a 90° -pulse [30].

The time constant characteristic T_1 depends on B_0 as well as on the mobility of the molecules in the observed medium (Brownian motion). For the human tissues, T_1 varies in a range of a few hundred of milliseconds to over a thousand of milliseconds for a field B_0 of 1.5T. The longitudinal relaxation is caused by the magnetic field fluctuations, which imply a dissipation of the extra

energy accumulated by the nuclei in their environment (lattice).

The second phenomenon is the transverse relaxation (or spin-spin recovery or **T₂ relaxation**). After the excitation, the transverse component of the magnetization of adjacent spins are in phase coherence. Afterwards, due to the field fluctuations related to the interactions between the spins, some will accelerate, while others will slow down (see Figure 2.11). The spins lose their phase coherence and the vectorial sum of their transverse magnetization declines exponentially with a characteristic time T_2 :

$$M_{xy}(t) = M_{xy}(0) \exp\left(\frac{-t}{T_2}\right) \quad (2.7)$$

In other words, the "transverse relaxation is the decay of transverse magnetization because spins lose coherence (dephasing)" [30]. It is called spin-spin relaxation because there is no energy transferred with the environment.

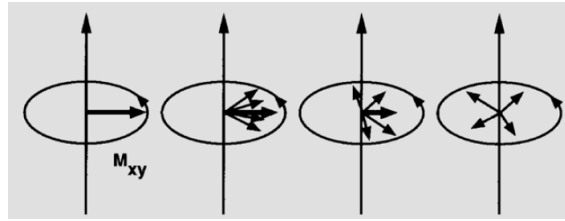


Figure 2.11: Illustration of the transverse relaxation due to the lost of phase between the spins [30].

For transverse relaxation, another phenomenon intervenes in addition to the fluctuations of the field; there are inhomogeneities in $\mathbf{B}_0$ because of the generator itself and the scanned tissues. This introduces a faster relaxation time than T_2 characterized by the time constant T_2^* :

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \gamma \Delta B_0 \quad \text{with } \Delta B_0 \text{ the amplitude of variation of } \mathbf{B}_0 \quad (2.8)$$

Measurement of the magnetic resonance signal

To measure the magnetic resonance, antennae must be placed around the scanned tissues, perpendicular to the axis of $\mathbf{B}_0$. In this configuration, they capture the variations of the magnetic field corresponding to the transverse component of the magnetization. Indeed, after an excitation of the medium (with a 90° -pulse for example), the component M_{xy} is maximum. Then it begins to decrease while the spins start to dephase. An antenna, such as a simple electric coil, captures the fluctuations of the magnetic field related to the variation of M_{xy} and the resulting electrical signal is called the Free Induction Decay (FID). This assembly is shown schematically in the Figure 2.12. The envelope of the FID is well influenced by the characteristic time T_2^* as explained previously.

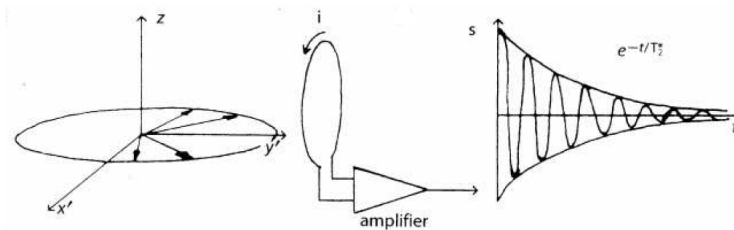


Figure 2.12: Phase shifting of the transverse magnetization in the rotating frame and measurement of the FID [25].

To be able to measure the relaxation T_2 , a little trick is used, called *spin echo*. This technique consists in exciting the system with a 90° -pulse at $t=0$. After this, the spins are out of phase and the FID disappears. After a time τ , a second RF pulse, a 180° -pulse this time, is transmitted. This wave makes the spins phase again and reveals an echo of the FID at $t=2\tau$. A re-transmission of a 180° -pulse all 2τ , re-echoes the FID, as shown in Figure 2.13. The envelope formed by the maxima of the MR signal and the echoes is influenced by the time T_2 and no longer T_2^* , as desired. The time delay between the 90° -pulse and the center of the echo is called the echo delay $TE = 2\tau$. After $t = TE$ the isochromats⁵ dephase again.

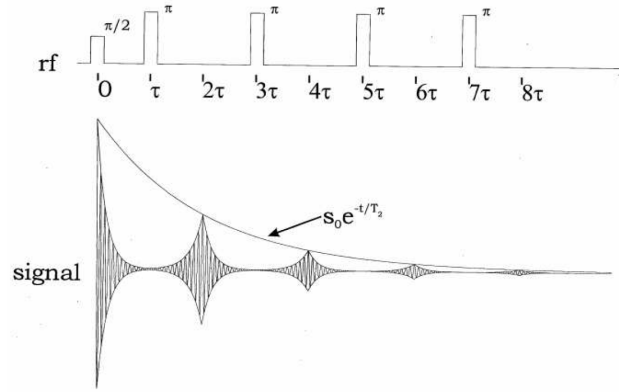


Figure 2.13: Magnetic resonance signal resulting from a 90° -pulse excitation followed by echoes induced by 180° -pulse phasing again all 2τ [25].

Inversion recovery

One must also be able to make the sequence of spin echoes T_1 -sensitive in order to measure this quantity, characteristic of the observed materials. This is done by emitting a 180° -pulse at a time TI before the 90° -pulse. This time TI is the inversion time and the transverse magnetization at the center of the echo is then given by the following formula:

$$M_{xy} = |1 - 2\exp(-\frac{TI}{T_1})|\exp(-\frac{TE}{T_2}) \quad (2.9)$$

Figure 2.14 shows the temporal sequence of emission of the RF-pulse and the sampling of the MR signal. The sequence is repeated at a period named the repetition delay (TR) in order to emphasize the emitted signal.

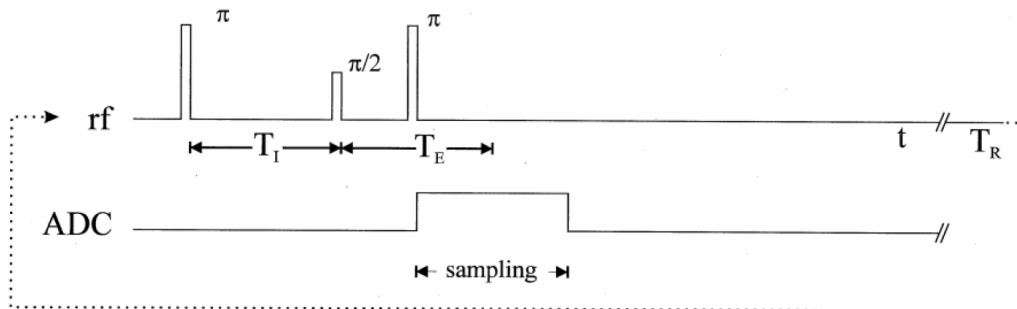


Figure 2.14: Time sequence of RF pulses emission and RM signal sampling using inversion recovery and spin echo techniques [25].

⁵An isochromat is an infinitesimally small volume of spins in which the magnetic field can be considered homogeneous

T1/T2-weighting

The parameters TE (echo time) and TR (delay time) can be adapted to modulate the influence of the T1 and T2 values as well as the proton density (PD) on the MR signal. This is called T1-, T2- and PD-weighting of the signal. Human tissues are visible on MR images thanks to the differences between their magnetic properties (Figure 2.15 illustrates the difference between the relaxation times of two tissues) and the weighting of the acquired signal.

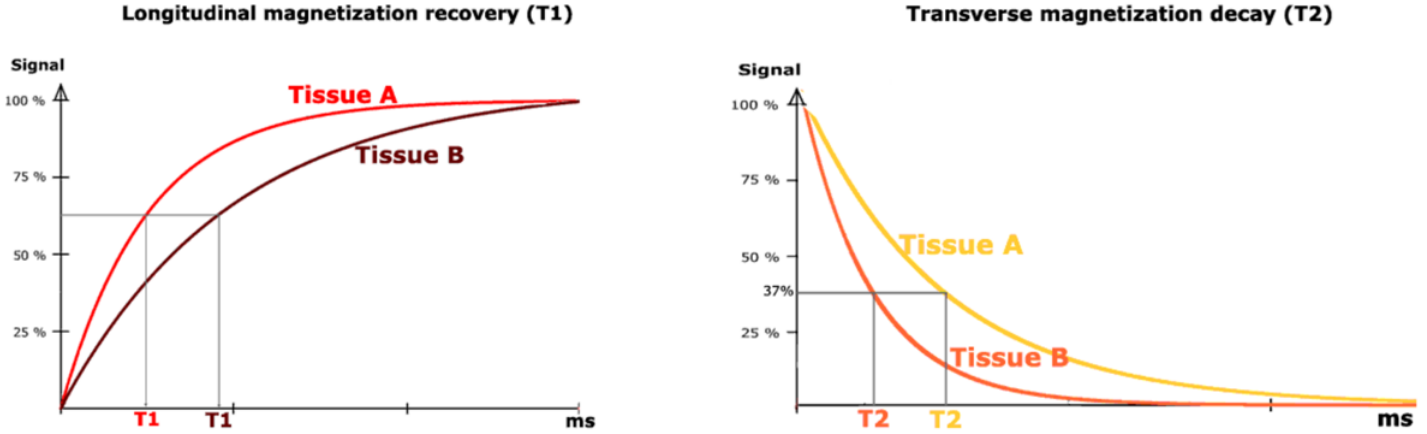


Figure 2.15: Graphical representation of T1 and T2 values in two different tissues [31]

To understand this mechanism essential for the image contrast (see application in Chap. 4, Sect. 4), the basic **spin echo** sequence will be considered (Fig. 2.16). It is important to have in mind that only perpendicular signals to the antennae may be collected which means that these latter are exclusively sensitive to transverse magnetization variations. Moreover, T1 relaxation and T2 relaxation are simultaneous.

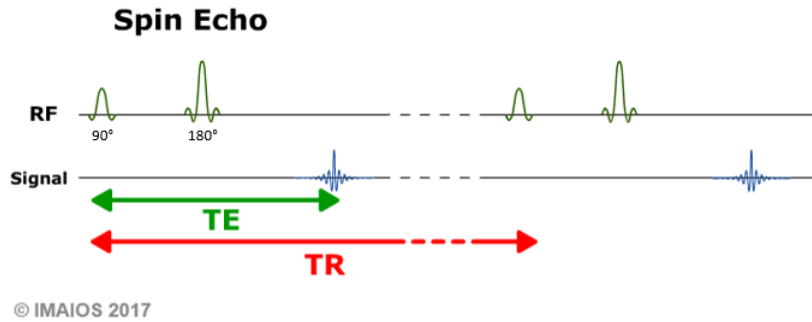


Figure 2.16: Excitation and inversion of proton spins in a spin-echo sequence [31]

Lets consider two tissues, tissue A and B, with different T1's as depicted on Figure 2.15 (left part). Thus, the recovery rate after the 90° RF-pulse in a spin-echo sequence will be different for each tissue. For a long TR (approximately 1500 ms), the longitudinal recovery in each tissue has the time to regain completely before the next excitation. However, if TR is short (approximately a third of a long TR) and, assuming that T1 of tissue B is longer than T1 of tissue A, the longitudinal magnetization of A will recover more than the longitudinal magnetization of tissue B. Then, the new excitation of the protons has a greater amplitude in tissue A than in tissue B. Eventually, the amplitude of the transverse magnetization, which is the measured quantity by the receiving coils, of tissue A will be higher after the next excitation, i.e. the signal from tissue A is more intense [31].

In general, short values for TR will enhance the differences in longitudinal magnetization (T1)

whereas longer TR values fade the T1 effect on the tissue contrast away. In the same manner, the duration of TE affects the T2-weighting of the signal. Long enough TE values enable to distinguish tissues on the basis of their transverse magnetization characteristic (T2) and shorter TE values alter tissue contrasts for this same characteristic [31]. Figure 2.17 summarizes these sequences.

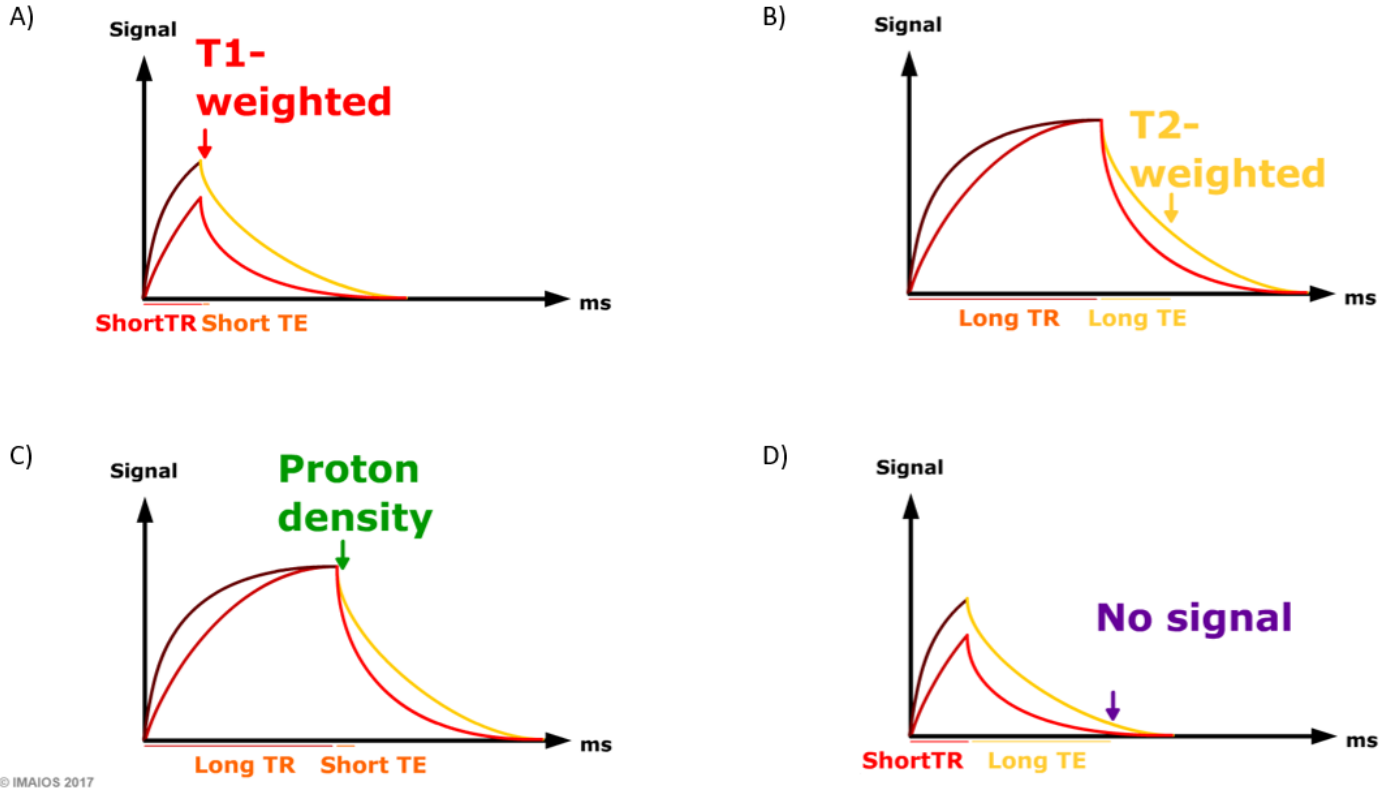


Figure 2.17: Evolution of the NMR signal through time in a spin-echo sequence for A) T1-weighted image B) T2-weighted image C) PD-weighted image D) no contrast image. It is important to recall that longitudinal and transverse magnetization recover simultaneously [31].

4.2 Image reconstruction from the magnetic resonance signal

It is therefore possible to characterize a material by collecting its specific relaxation times T1 and T2 in response to RF-pulse sequences while being immersed in an intense magnetic field. In the second part of this chapter, the reconstruction of the magnetic resonance image will be detailed, together with the instrumentation necessary for the application of this theory.

Instrumentation

To perform an MRI, it is necessary to produce intense homogeneous magnetic fields and to measure the magnetic resonance signal. It therefore requires a specific material.

First, the main magnetic induction field $\mathbf{B}_0$ must be produced and be as constant and homogeneous as possible. This is done, most of the time, with the use of superconducting electromagnetic magnets. These magnets require liquid helium cooling (and the corresponding safety system in case of helium heating). A schematic diagram of the main coils of the MRI is shown in Figure 2.18. For medical use, the main field is equivalent to 1.5T to 3T.

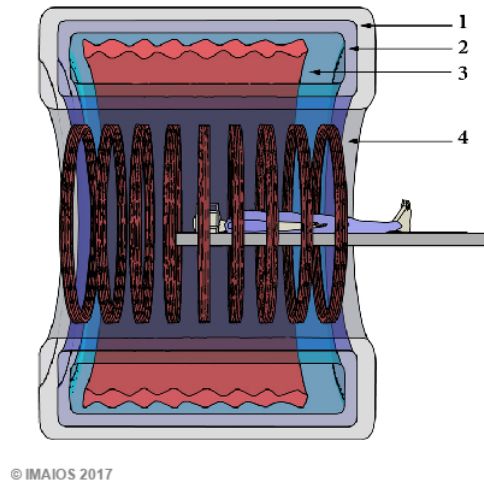


Figure 2.18: Schematic of the MRI scanner : 1) External enclosure 2) Cooled enclosure 3) Supraconductive coil 4) Shim coils [31].

Secondly, it is necessary to add magnets to create field gradients. They create fields much weaker than the main coil, the coefficients G of the equation 2.10 being typically of a few mT/T . The coils of the gradients are placed orthogonally as shown in the Figure 2.19.

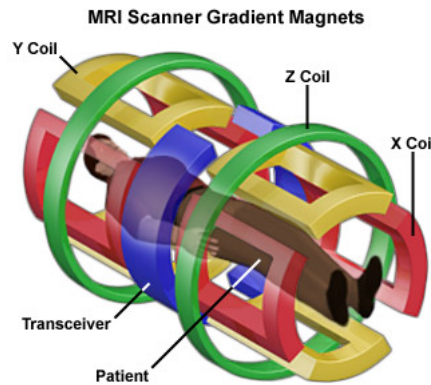


Figure 2.19: Schematics of the shape and placement of the gradient coils. [32]

In addition to these coils, RF receivers, transmitters and corresponding amplifiers are required. In real conditions, MRI is performed in a room insulated by a Faraday cage to avoid disturbances from the outside, such as radio waves. The whole system of control, acquisition and processing of data is in an adjacent room: the control room. There are hoses, called waveguides, that pass through the walls of the room, allowing cables or other necessary elements to enter the room without disturbing the homogeneity of the magnetic fields. These waveguides are important in this project and their use will be detailed in the remainder of this document.

Finally, the MRI room is equipped with a surveillance camera to keep a visual control of the patient during the image acquisition, as well as domestic power supplies (50Hz, 220V).

Gradient field

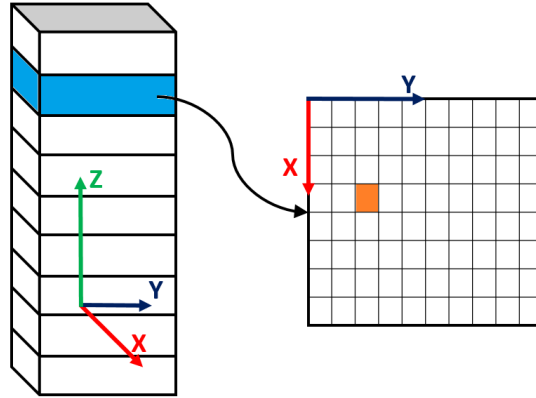


Figure 2.20: Splitting of the analyzed volume into superpositions of slices (in blue) divided into voxels (in orange).

At this point, it is necessary to be able to link the information concerning the observed matter with its spatial position. First of all, the volume to be scanned is cut into slices perpendicular to the Z axis. Each of these slices corresponds to an image and the stacking of these images recreates the 3D view of the complete volume. In addition, each slice is divided into voxels according to their position in (X,Y). The Figure 2.20 schematizes this division.

In practice, the spatial information is encoded in the MR signal. This is done by the application of magnetic field gradients. These fields are oriented in the Z axis, but vary linearly with the position along the axis. They are denoted G_z for the Z axis for example. The main field is now:

$$\mathbf{B} = \mathbf{B}_0 + (G_x x + G_y y + G_z z) \mathbf{I}_z \quad (2.10)$$

The modification of the intensity of the main field as a function of the position implies that the Larmor frequency also varies with the position:

$$f_0(x, y, z) = \gamma[B_0 + G_x x + G_y y + G_z z] \quad (2.11)$$

Spatial coding

The first step to build an image is the selection of a slice of the system in the Z direction. This is done by using a Z-gradient field. Indeed, as explained above, the application of such a field will modify the Larmor frequency of the spins, which will be linked to their position in Z. The excitation of the system with a RF pulse at a fixed frequency will thus induce resonance only in a part of the volume: a Z-slice whose Larmor frequency is the same as the frequency of the RF pulse.

Figure 2.21 illustrates this principle: for a field gradient of G_z fixed, the choice of a frequency for the excitation pulse f_1 selects the left slice whose Larmor frequency $f_{Larmor1} = f_1$. For an excitation with frequency $f_2 > f_1$, the slice moves in the Z-positive direction. Indeed, the Larmor frequency of a slice is in this case of the shape $f(z) = B_0 + G_z z$ and an excitation frequency $f_2 > f_1$ corresponds to a slice of $f_{Larmor2} > f_{Larmor1}$ and therefore at a more distant Z-position.

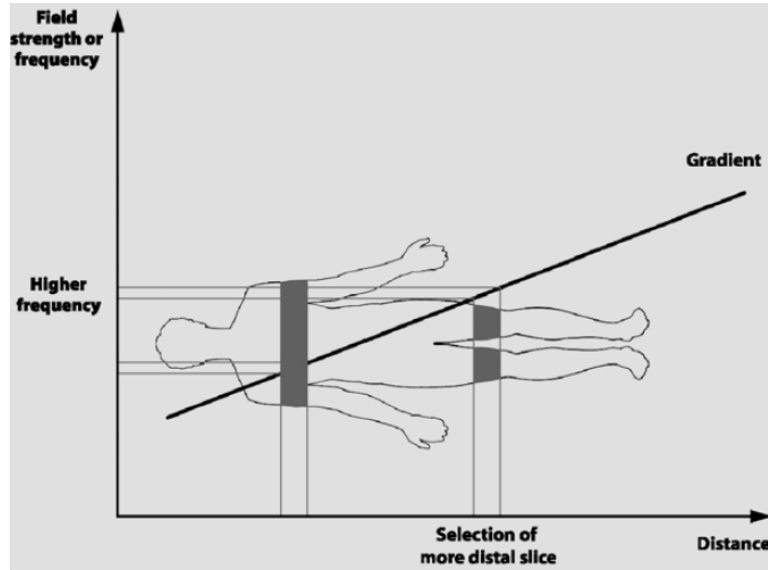


Figure 2.21: Selection of a Z-slice by the application of a Z-gradient field and with a RF pulse of fixed frequency. [30]

In practice, the use of a RF wave of the cardinal sinus truncation type for the excitation makes it possible to excite a slice of a given thickness and with a pulsation of a finite time.

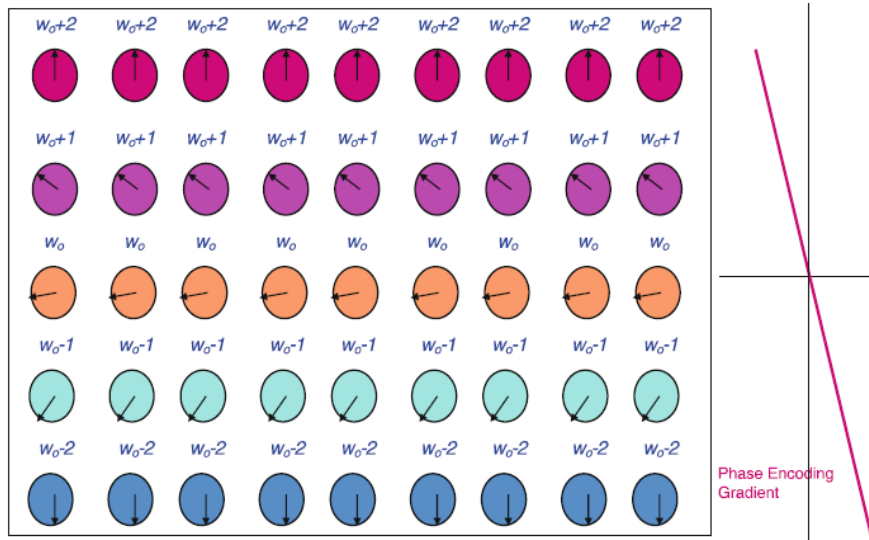


Figure 2.22: Visualization of the impact of the application of a Y-gradient on the rotation speed of the spins. [29]

After the excitation of a Z-slice, it is now necessary to code the spatial information (X,Y). To do this, the X position is encoded in frequency and the Y position is encoded in phase. First, after selecting the Z-slice, a Y-gradient is applied. The spins at different Y's will then rotate at different frequencies, as shown in the Figure 2.22. At the precise moment when the gradient disappears, the spins on a same line will all have the same phase in the Y-direction, while they will all be out of phase in the X-direction. Thus, when a y-gradient replaces the X-gradient, the spins of an X-line will all be out of phase, but with the same frequency. Conversely, for a line in Y, the spins will have different frequencies, but the same phase.

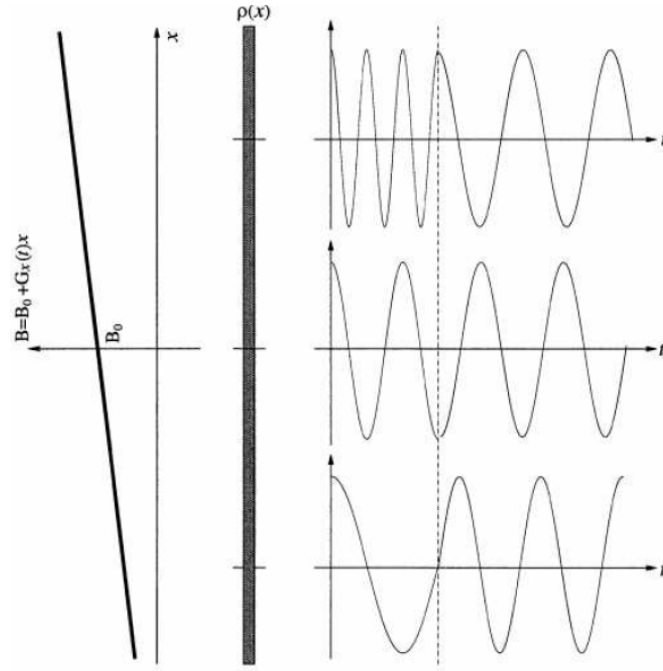


Figure 2.23: MR signals of three infinitesimal volumes placed on a Y-line to visualize the transition between the application of the phase and frequency gradient which induces a phase shift of the MR signal. [25]

This transition is visible in the Figure 2.23, which shows the MR signal of three infinitesimal volumes with the same position Y but a different position X. In a first step, the phase gradient is applied. The spins rotate at different speeds because they have different x-positions and their Larmor frequency depends on the field, which itself depends on the x-position due to the phase gradient. When the phase gradient stops, replaced by the frequency gradient, the spins have the same frequency because they have the same y-position but are out of phase due to differences in rotation velocities in the first part of the transmission sequence.

Image reconstruction

Once the signal contains the spatial information, it is possible to recreate the image from the MR signals. In simple image sequences, the information is encoded line by line in the Fourier plane, called the k-space, by increasing the phase gradient in stages. For each line, the information is sampled in the X direction. The position at X and Y is found with demodulation by a 2D inverse Fourier transform of the matrix.

This way of recovering the image has a non-negligible acquisition time of several minutes. For example, for an image of 256 lines, with a repetition time $TR = 2000\text{ms}$ (spin echo sequence), the acquisition time is given by:

$$T_{acq} = N_y TR = 512 \text{ s} = 8 \text{ min } 32 \quad (2.12)$$

In practice, various methods are used to reduce this acquisition time, but this is always a constraint to be taken into account.

Image quality

Image quality is dependent on the characteristics of the magnetic field B_0 , the MR signal and the noise. Artifacts may deteriorate the image as it will be described in the next section. The quality of the image is quantified in terms of the signal-to-noise ratio (SNR), which is described

by equation 2.13:

$$SNR \propto \Delta V \sqrt{\frac{NEX N_x N_y}{BW_r}} \quad \text{with } BW_r = \gamma G_x W_x \quad (2.13)$$

where $\Delta V = \Delta x \Delta y \Delta z$ is the voxel volume, NEX the average number of excitations, $N_x \times N_y$ the size of the image matrix and BW_r the read out bandwidth (= frequency encoding range). The quality of the image increases when the SNR increases. Typically, SNR is modulated by increasing the size of the voxel, i.e. by varying the thickness of the slices (Δz) or the spatial resolution (Δx and/or Δy). In clinical examinations, the contrast-to-noise ratio (CNR) is preferred as it is a metric of the difference between signal intensities :

$$CNR = S_1 - S_2 \quad (2.14)$$

The quality of the image can be enhanced by employing several sequences over the same slice but this has a negative impact on the length of the acquisition time. A compromise must be found by the user between image quality and acquisition time.

Image sequences

Gradients and RF-pulses can be combined in various orders to enhance the signal from a given tissue and to accelerate the acquisition process. These combinations are called image sequences. In line with the former explanations, RF pulses are essential for the NMR excitation and gradients enable spatial encoding. The sequences can be characterized by the signal reading, which depends on the type of echo recorded (gradient echo or spin echo). Some sequences will even be a mix a gradient echoes (GE) and spin echoes (SE). Parameters of a sequence are defined as the echo time (TE), the repetition time (TR), the flip angle (α), the turbo factor⁶ and the field of view matrix. The choice of the parameters is dictated by the necessity to find the best compromise between spatial resolution, contrast and speed for each given situation.

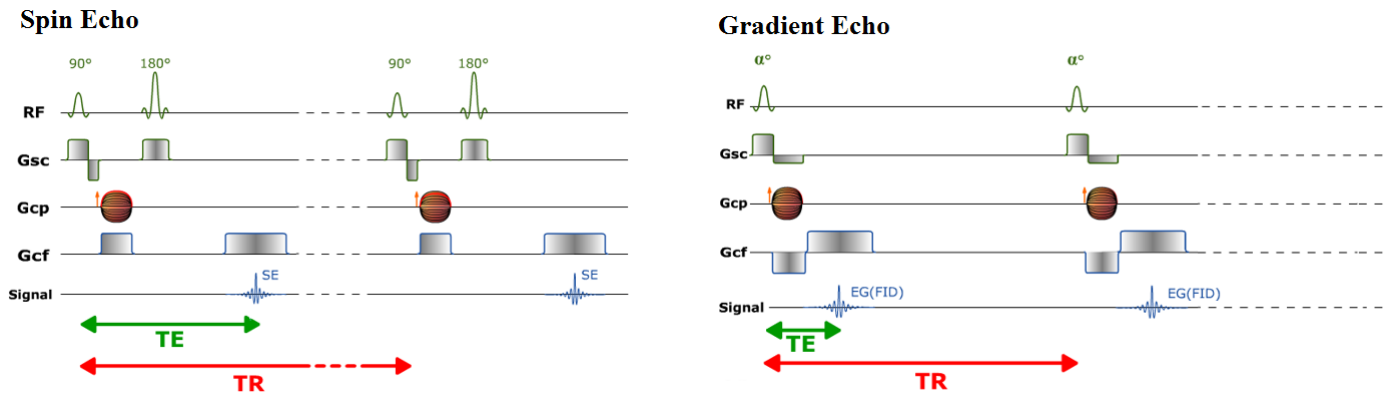


Figure 2.24: Basic Spin Echo (SE) sequence (left) and Gradient Echo (GE) sequence (right). Gsc is used for *slice selection gradient*, Gcp for *phase encoding gradient* and Gcf for *frequency encoding gradient* [31]

In the case of tumor tracking in real-time, the balanced steady-state gradient echo sequence (named sBFFE or True FISP on Philips and Siemens scanners respectively) is being evaluated. Gradient echo sequences are characterized by the absence of a 180° rephasing pulse (typical of SE sequences) and by a low flip angle (lower than 90°). This latter particularity enables a faster longitudinal magnetization recovery that allows to decrease the TR and TE of the sequence, i.e. to accelerate the scan time. The echo is obtained by applying a dephasing gradient before the

⁶The turbo factor is the number of echoes received in the same repetition (during TR)

readout gradient since no rephasing pulse is used. Consequently, to the reduction of the TR, a residual transverse magnetization is present in the signal. It is defined as the steady-state and it will participate to the contrast in the image. However, a phase shift related to fast liquid flows may disturb the phase encoding of the steady-state. Therefore, balanced gradients are applied in the three directions to annihilate the phase shift. "*With these sequences, we obtain ultrafast [roughly 0.5 to 0.1 second per slice] and robust imagery with a liquid / tissue contrast and an excellent signal to noise ratio*" (IMAIOS [31]).

4.3 Artifacts

The various types of artifacts developed below form a non-exhaustive list of the most common problems encountered in the use of MRI, starting in particular with movement artifacts that are critical to this master thesis.

Motion artifacts

Movements are the most frequent source of artifacts, as an imaging sequence can take several minutes. There is :

- the random movements creating a diffused blurring in the frequency coding direction,
- the periodical movements (respiration, heart pulsations, peristalsis⁷) which create ghosts in the phase coding direction.

It is in the direction of the phase coding that the movements are problematic because the repetition of the acquisition in this direction is rather long (ranging from a hundred milliseconds to seconds), while the coding of frequency is done at a speed of a few milliseconds, which is much faster than the physiological movements and therefore is not a problem.

For periodic movements, phantom images (partial copies of the object) are formed, linearly repeated in the phase encoding direction. The phase or amplitude of the magnetization changes between two acquisitions and the Fourier transform does not reconstruct the image correctly, producing those ghosts that are brighter or darker than the original image. The intensity and deviation between the ghosts will depend on the amplitude of the motion and its frequency with respect to the frequency of the phase sampling.

Different solutions are possible. For breathing, the simplest is an image taking while the patient holds his or her breath (for sequences of less than 30 seconds). The use of sedation or general anesthesia is also possible.

Another solution is to ask the patient to breathe as regularly as possible and to take the image periodically at the same phase of the breathing cycle. The diaphragm is then in the same position for each sampling and there is therefore no movement between two taps. However, this increases the acquisition time. This method is also used to remove artifacts due to cardiac movements.

A third method consists in following the movement of the diaphragm and compensating for the effects of respiration on the basis of the position of the latter by modifying the gradient fields. The main disadvantage of this method is the decrease in the quality of the high frequencies of the image and thus a blur on the abrupt contrasts.

Otherwise, a compression belt can be placed around the scanned area for the case of an abdominal MRI. This belt will compress the organs and reduce the amplitude of movement of these, forcing the patient to breathe by swelling the chest and not the belly.

Finally, it is possible to suppress the signal from the tissues at the origin of the artifacts by the use of pre-saturation pulses.

⁷Unconscious muscle contractions that push the alimentary bolus into the digestive system

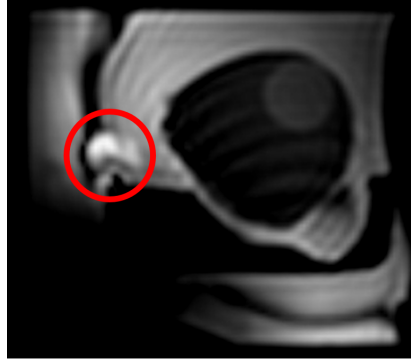


Figure 2.25: Artifacts due to the motion of the water

In the case of our phantom, the purpose is to observe the movements of the breathing. The chosen solution is therefore to use the fastest imaging sequences possible to have the lowest breathing influence. This reduces the quality of the image, but it is still possible to track the tumor on this kind of videos. However, the Figure 2.25 shows that an artifacts due to the motion of the water inside the phantom can still appear.

Magnetic susceptibility

There are two possible kinds of magnetic field disturbance: the external inhomogeneities of the main field $\mathbf{B}_0$ and the internal local distortions. The former are no longer a problem thanks to the shim coils which are sufficiently adjusted by the manufacturer. On the other hand, the latter are related to the susceptibility of the different materials in the field of vision. As a reminder, the magnetic susceptibility χ links the induction magnetic field in which a material is placed and the resulting magnetization :

$$\mathbf{M} = \chi \mathbf{H} \quad (2.15)$$

However, the magnetic susceptibilities of the different materials are different, which implies artifacts at the interfaces between them, as between air and human tissues (see Figure 2.26). These artifacts are due to magnetic field distortions that lead to phase or frequency errors and therefore to poor image reconstruction.

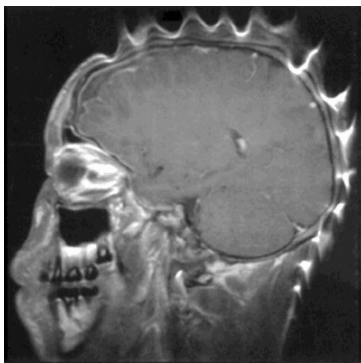


Figure 2.26: Artifact at the interface between skull and air due to differences in susceptibilities of the two media. [33]

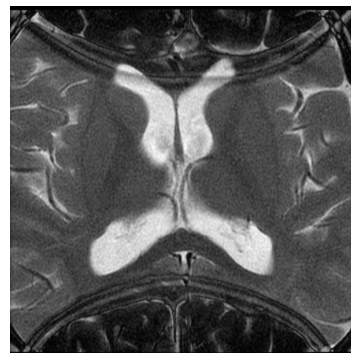


Figure 2.27: Illustration of the aliasing phenomenon from the outside of the field of view inside the image, for a cut of a skull. [34]

Aliasing

Aliasing occurs when the image of the tissues outside the field of view seems to be folded within the area of interest. This type of artifact can be seen in the Figure 2.27. This can occur in both directions of the phase or frequency encoding because it is due to a subsampling of the

k-space for the Fourier transform. Different methods are used to avoid this kind of artifact, such as over-sampling or by attenuating the signals from outside the field of view (with the use of saturation pulsations or surface coils).

Chemical shifts

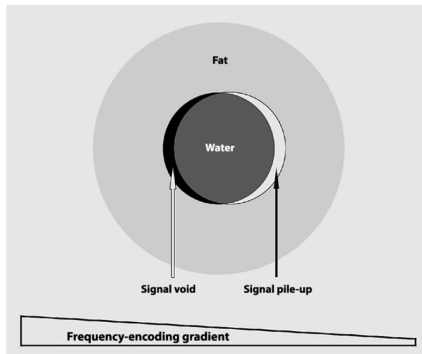


Figure 2.28: Offset between image of water and grease (or silicone) causing chemical shift artifact. [30]

This kind of artifact occurs in areas between fat or silicone and water because the resonance frequency of protons varies depending on the molecular environment. There are two possible consequences on the image: poor spatial recording of responses to material excitation or suppression of the signal at the interface between materials. The first consequence is distinguished on the image by a shift of the image of the water relative to that of the grease or the silicone, creating a dark zone on one side and a bright on the other one, as seen on the Figure 2.28. The second consequence is recognizable by the formation of a dark zone at the interface between the materials.

Chapter 3

Design of the solution

This chapter traces our design process and the decisions taken when establishing the solution. We followed the methodology of prescriptive design created by Pahl and Beitz and taught by Professor Benoît Raucent in the lecture *Machine Design* [35] at the Université Catholique de Louvain (UCL). This method ensures the progression of the design through a series of intermediate steps, essential to the development of a prototype. In this chapter, the impact of the participation in the innovation classes [LFSA2212], followed by two of us (Arnould GEELHAND and Tanguy THIBAUT) during the academic year, will also be commented as it has played a major role in the design approach.

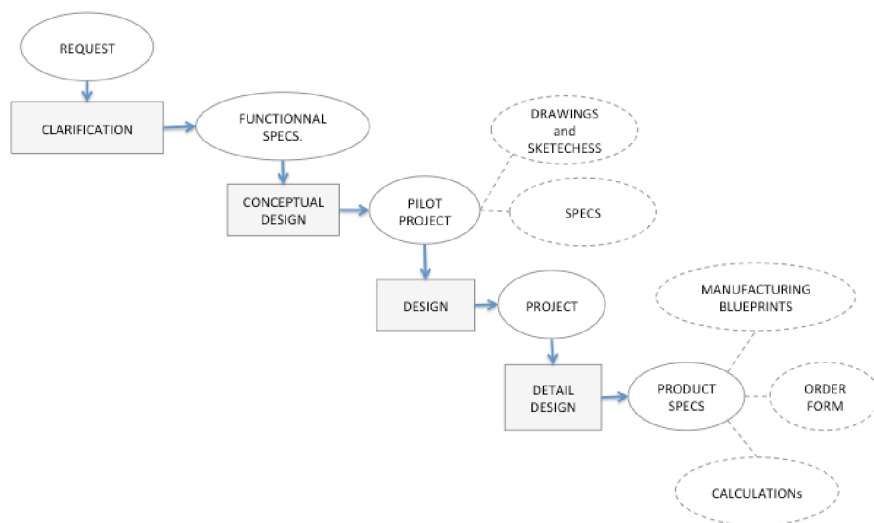


Figure 3.1: Design Steps [35]

As mentioned before, the approach is greatly inspired from the process recommended in the lecture *Machine Design* [35] (see Figure 3.1). However, the reader must keep in mind that the design method is an iterative process sometimes made of trials and errors. Furthermore, the clarification of the demand and the design are often bound together and are not two steps as independent as they may appear. In this section, the five most important stages shall be presented :

- Clarification of the demand,
- Establishment of the state of the art of the existing or possible solutions
- Search and design of several solutions

- Choice of the solution
- Description of the implementation of the solution.

1 Innovation Classes

Funded by LhoistTM and AGCTM, the innovation classes [LFSA2212] aim at training future engineers to better identify an innovative idea and to improve communication and teamwork to develop a project in a multicultural and multidisciplinary context. The classes are divided in three distinct parts, described below : the kick-off, the courses during the year and the trip. This part of the chapter also contains the benefits gained from this course and their implications on our master thesis.

Kick-off

The kick-off introduced the innovation classes with a challenge proposed by an industry. In six hours, each team had to come up with an innovative solution, supported by a proof-of-concept. It was the first opportunity to meet the supervising staff as well as the members of our team with whom we were going to work for the rest of the semester. Our team was composed of people with different educational backgrounds (essentially engineers and architects) and, especially, with various cultural backgrounds. Indeed, there were, in our team, two Erasmus students, one from Sweden, one from Japan, and a former company executive, father of a family. The experience was quite intense and asked us to use our best skills in brainstorming, communication and leadership in order to meet the deadline.

Innovation Classes

The rest of the course provided an opportunity to deepen our knowledge by attending a series of presentations from external stakeholders on topics such as brainstorming, problem identification, TRIZ methodology and public communication. In parallel, AGC submitted to the students of the course another challenge. The problem was to find an innovative way of convincing the public to replace their obsolete windows with double-glazed or triple-glazed products. This issue was a great way to discover the innovation process from the identification of the need to the implementation of a concrete solution. As far as this thesis is concerned, these learning outcomes have helped us to master the iterative process of innovation and apply it to our own project.

The trip

During the third part of the course, we had the opportunity to travel to an university abroad to see how innovation was done there. Therefore, we left 10 days for the Texas A & M University. First, we were able to take part in an innovation contest called the *Aggie's Invent* where the goal was to set up a start-up with a valid product and a business plan on the theme "Internet of Things" in 48 hours only. Secondly, we were fortunate to meet and discuss our master thesis with a large number of experienced entrepreneurs. These meetings have been of great help for our master thesis, because our spokesperson shared with us a lot of valuable resources such as tips on how to establish specification, contact with resourceful people, visit of MRI infrastructures and advice about the project. Finally, it was also the opportunity to discover the entrepreneurial mentality of the United States by attending a few courses and by visiting a local start-up incubator.

2 Needs and requirements

Since our phantom will be used by Damien Dasnoy-Sumell in the context of his PhD thesis (See Chapter 1, Section 2.2), under the supervision of Professor Benoît Macq, the first step in the design process was to establish a clear set of specifications, combining their requirements and the limited resource of our master thesis. The final version of the needs and requirements, accepted by all parties, is attached in Appendix B. It is structured in two complementary parts, the main functions and the constraint functions.

Main functions

Here are the four main functions that our device had to fulfill.

- **MF1 : Mimic the motion of a tumor located in the liver under the influence of the human breathing.**

The phantom is intended for the validation and the calibration of mobile tumor tracking methods, notably developed by Damien Dasnoy-Sumell. The principal objective of the phantom is to set a liver tumor surrogate in motion following the human respiration pattern in terms of frequency and amplitude. Due to the proximity of the heart (on the other side of the diaphragm), the liver is also influenced by the cardiac cycle and the blood circulation. When the patient is under apnea, the amplitude of this phenomenon can reach up to 5mm [36]. However, in our case, the patient, that Damien Dasnoy-Sumell would like to mimic, breathes normally. Under this assumption, we neglect the effect of the cardiac cycle on the motion of the liver. The liver movement is also slightly influenced by peristalsis, the contraction of the intestine during the digestion. Again, this phenomenon is neglected because its amplitude is less important than the one related to the respiratory cycle.

- **MF2 : Give the 3D position of the tumor at all time.**

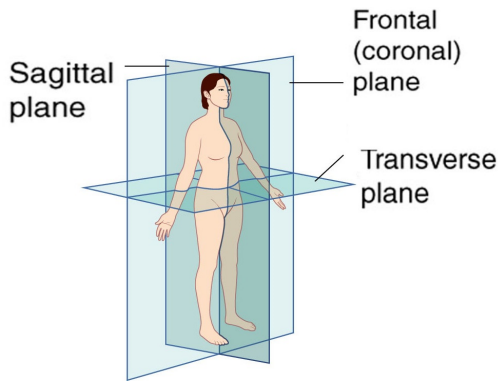


Figure 3.2: Different body planes

To confirm the accuracy of the localization of the tumor via the MR images and the tracking algorithms, our device must be able to give the position of the target tumor with a 1 millimeter precision, using another method than magnetic resonance imaging. This simultaneous tracking system shall evaluate the movements of the tumor in the coronal and the sagittal planes, depicted on Figure 3.2.

- **MF3 : Mimic the contrast values of the upper-abdominal tissues of a human.**

Since the research of Damien Dasnoy-Sumell is focused on the tracking of soft tissue tumors, especially located in the liver, the phantom has to accurately represent the upper abdominal section of the human body. Benoit Macq and Damien Dasnoy-Sumell required that the liver, the pancreas and the stomach should be represented in the phantom. Moreover, in order to ensure the contrast between the tissue surrogates on the MR images to be

similar to those of real organs and tumors, the relaxation times T1 and T2 (see Chapter 2, Section 4.1) must be as close as possible to the reality.

- **MF4 : Mimic the mechanical interaction between the organs of the upper-abdominal region of a human.**

The organs must move in accordance with the basic human body mechanic. In particular, the organ deformations must be taken into account, in addition to the translation and rotation motions.

Constraint functions

In addition to these main functions, the phantom must also deal with some constraints; the major one being the MRI compatibility of the system. Any device, or part of it, introduced in the MRI enclosure, must fully respect several criteria :

- Any ferromagnetic material is forbidden from entering the room (which acts as a Faraday cage) where the MRI machine is placed, otherwise it could be dangerously attracted by the intense magnetic field of several Teslas and it could degrade the scanner's environment. Yet the absence of ferromagnetic elements is not enough to ensure MRI compatibility. Indeed, to be considered as "MRI compatible", a device shall not present any additional risk to the patient or other individual (MRI-Safe). Moreover, neither the quality of the diagnostic information, nor the operations of the device shall be significantly impaired by the device itself and the MR system respectively. The induced currents by the varying electromagnetic fields, leading to an over-heating of the conductive elements, are one example among others of potentially detrimental interactions within the MRI enclosure. A list of acceptable materials can be found on the mrisafety site ¹.
- The size of the device must be suitable for the environment where the magnetic resonance scanner is installed. This one is placed in the middle of a room about 7x7 meters. To be scanned, a part of the phantom must be able to enter inside the electromagnet, a cylinder of 60cm of diameter, and must be recovered by an antenna. Another part of the device may be placed outside the room, in the control room or corridor. A copper tube of 6cm in diameter ensures the connection between the interior and exterior of the room. Regarding the antenna, there exists many types for all parts of the body. In upper-abdominal examinations, a torso antenna, which consists of two flexibles plates, surrounds the patient.

3 State of the art of MRI phantoms

"The purpose of the phantom dictates both its form and its composition. When selecting or designing a phantom, one must carefully consider the materials to be used, the physical shape and how these will affect what is trying to be measured in the situation of interest. There is an immense variety of phantoms available for any given application and a proper selection of the phantom is dependent entirely on the situation in which it is to be used" (DeWerde et al., 2013) [37].

Generally speaking, phantoms are used to represent the human body in medical imaging and health physics [37]. For the medical imaging, they can be categorized in two main families : **dosimetry phantoms** and **imaging phantoms**.

¹http://www.mrisafety.com/TheList_search.asp

The purpose of the former ones is to assess the dose delivery from an ionizing source to the device in order to simulate medical treatment procedures. These phantoms have been developed essentially to avoid exposing human people to unnecessary radiations. They offer a variety of designs, from the simplest ones, such as water tanks, to more complex structures. As computer technologies have become very efficient, computational phantoms have been popularized to evaluate radiation treatments as well.

Concerning imaging phantoms, they are used to establish the limits of imaging systems and to give qualitative feedback of the imaging protocols. The development of our phantom is in line with the research in this field of application.

Our research on existing devices was mainly focused on the three following points :

- MRI compatibility
- Dynamic phantoms
- Phantoms that realistically reproduce the shape and contrasts of abdominal organs.

Our findings can be listed in two different sections. The first one concerns commercialized phantoms answering one or more of the above criteria. The second section gathers experimental devices developed in research labs and addressed to imaged-guided applications. Though this list is not limited, the restricted amount of phantoms described reflect the innovative character of dynamic phantoms for MRI.

3.1 Commercialized phantoms

For phantoms already existing on the market, there are essentially three companies that offer dynamic phantoms and a dozen of companies that offer static phantoms. Four of these phantoms, representative of the different solutions existing for our main functions, will be presented in the following section.

Dynamic phantoms

The first company is called *Vital Biomedical Technologies* [38]. They designed an interesting product, which is a fully programmable, MRI-compatible with two-degrees of freedom actuator (translational and rotational) as shown in Figure 3.3. The user can define the trajectory via a specific software and then load it into the control system with a micro SD card. Output data are collected by a USB cable. The motor is controlled by a control unit located outside the MRI room. Little information is given regarding the activation other than the fact that it is based on ultrasonic motors (also called piezoelectric motors²).

²a piezoelectric material is a material that deforms when submitted to an electric field and, conversely, creates an electric field when it is constrained

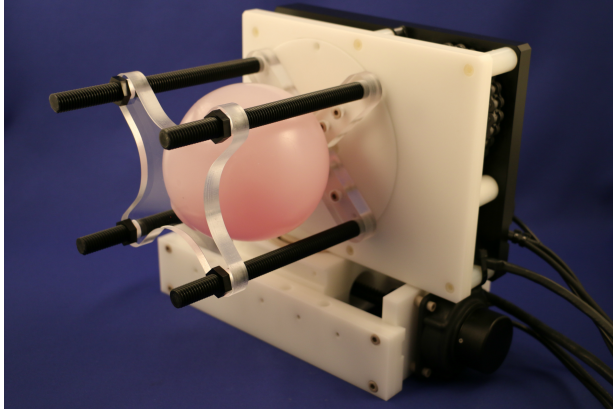


Figure 3.3: VBT MRI Compatible 2-Dimensional Motion Stage [38]



Figure 3.4: The programmable QUASAR™ MRI Motion Phantom [39]

The second dynamic product was developed by QUASAR™ [39]. It has the ability to do a translational movement as well as a rotation along the same axis in a cylinder. The latter is inscribed in a larger container of oval shape. A fictitious tumor may be placed inside the mobile part. The cylinder and the container may be filled with any contrast medium. The control is done via a computer placed outside the room, by entering the curves in the appropriate software.

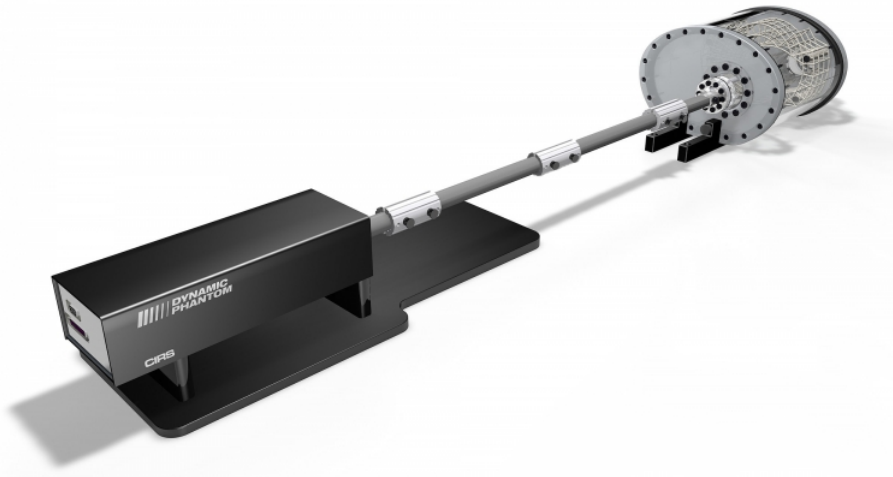


Figure 3.5: MRI-LINAC Dynamic Phantom [40]

The last dynamic phantom (Figure 3.5) is produced by CIRS (Computerized Imaging Reference Systems), the world's leader in phantom manufacturing [41], and is not suitable for machines running above 1.5T. Similarly to the preceding device, a translational and a rotational movement can be induced to a cylinder. This one is also contained in a box having the overall shape of a thorax and filled with a gel. However, in this case, the actuation is ensured by a long rod connected to an electric motor concealed in an Faraday cage made of anodized aluminum. It is placed far enough from the isocenter of the scanner to ensure MRI security as well as image quality.

An existing solution for X-rays scanner worth mentioning here is to transform a static phantom into a dynamic phantom by placing it on a moving platform [42].

Static phantoms

There are many different types of static phantoms. The specifications require to simulate as accurately as possible the contrast as well as the mechanical properties of the different organs. Therefore, this section is devoted to a device that have attempted to realistically mimic the human body according to these criteria.

The phantom presented here was developed by YEZITRONIX Group Automation & Control Industries [43]. It is a MRI-compatible prostate simulator, used for learning and testing operations procedures such as ultrasound-guided surgery, needle biopsy, and radiation implantation 3.6.

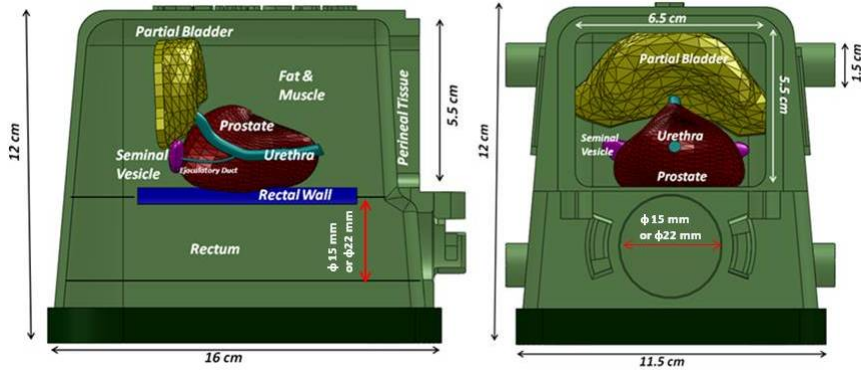


Figure 3.6: YEZITRONIX Multi Modality Prostate Phantom Model (US-MRI-CT) [43]

This device is very interesting in the way it managed to model the physical properties of the organs, their contrast and their 3D shape. To do this, they placed a series of fake organs in a PVC enclosure containing a gel similar to fat and muscle. As stated in the specifications of the phantom :

"All phantom tissues mechanical properties are approximated to human tissues. All prostate phantom layers mimic the tissue behaviour (dynamics) when pierced. When for example a needle is piercing the Multi-Layer prostate phantom construct, it will generate a "Haptic Feedback (tactile)" to the user, simulating the real human tissue during biopsy procedures." [43]

"Multi-layer material – each tissue or organ is independent and has its own characteristics defined by a real 3D shape, gray level and mechanical properties" [43]

3.2 Experimental phantoms

Researches are still led to develop new phantoms corresponding to the requirements of the actual technologies to be tested and validated. Again, four experimental phantoms representative of the existing mobile or anatomical phantoms for MRI are detailed in the following section.

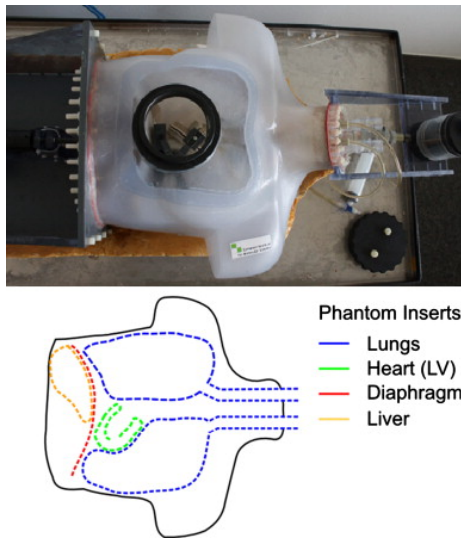
Abreu et al. - PET/MRI motion correction phantom

Figure 3.7: Photography (top) and schematic design (bottom) of the human torso phantom [44]

In 2013, the University of Münster (Germany) has developed this custom-built human torso phantom that can simulate the respiratory and cardiac motion [44] (Figure 3.9). It has been designed for PET/MRI data acquisition thus it is fully MRI compatible. To mimic the respiratory motion, the phantom inflates two synthetic lungs made of silicone. A 2 cm motion range is induced to the diaphragm by a pneumatic piston, controlled using LabVIEW™ (National Instruments, USA). Cardiac motion is simulated as well by inflating the inner cavity of a ventricle model with water. For the organs, compartments are filled with Fludeoxyglucose and different percentage of a contrast agent^a.

^aLumirem® is a negative contrast agent that, when ingested, darkens the stomach and intestine. <http://www.mr-tip.com/serv1.php?type=db1&db=Lumirem>

Neumann et al. - CT/MRI phantom for image-guided thorax interventions research

More recently, the searchers from the Medical Faculty Mannheim of Heidelberg (Germany) have published their achievements concerning the development of a phantom to assess the imaging techniques in use for image-guided interventions. They presented a modular, anthropomorphic MR and CT thorax phantom with insertable modules representing lung, liver, ribs and additional tracking spheres. The modules possess T1 and T2 values comparable to human tissues and follow 3D trajectory similar to human breathing motion [45].

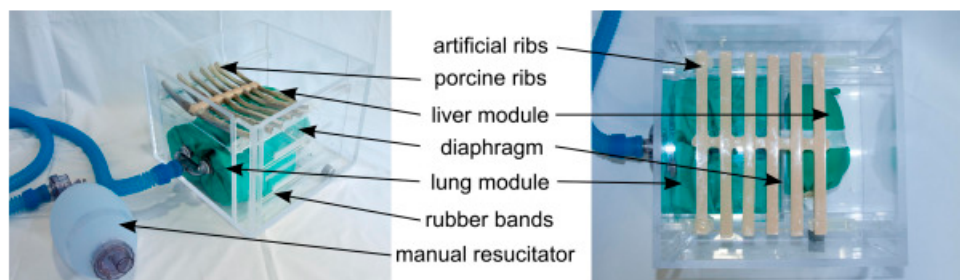


Figure 3.8: Overview of the phantom developed by Neumann et al.

Nieburh et al. - Multi-modality deformable phantom for image-guided radiotherapy

In parallel to Neumann et al.'s research, the division of medical physics in radiation oncology of the German cancer research center (Heidelberg, Germany) have implemented a multimodal tissue surrogate phantom to simulate image-guided treatment by radiotherapy. The soft tissue as muscle, prostate, and tumor were achieved using agarose gels in combination with a gadolinium-based contrast agent and NaF. Adipose tissues were represented with vegetable oil. Inner bone was realized using Vaseline and K₂HPO₄. *"Anthropomorphic shapes of bone and organs were realized using 3D-printing techniques based on segmentations of patient CT-scans."* (Niebuhr NI, 2016 [46])

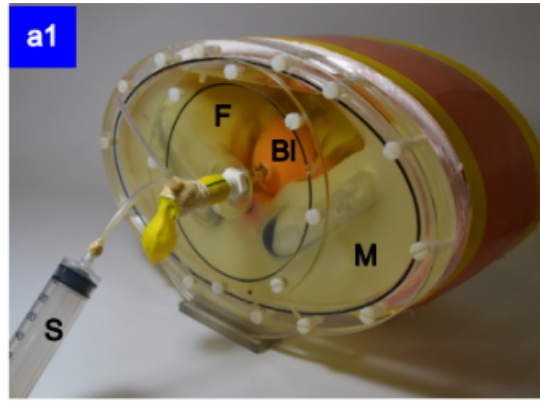


Figure 3.9: Overview of the phantom developed by Nieburh et al. [46]

de Tillieux et al. - Mimicking respiration-induced artifacts phantom

The Institute of Biomedical Engineering at Polytechnique Montreal has developed an experimental MRI compatible phantom in order to study the respiration-induced artifacts in spinal imaging (see Figure 3.10). It consists of a box of Plexiglass filled with water. An ex vivo spine is placed in the bottom of this box and two balloons – that can be inflated and deflated with air – simulate the lungs. The inflation system, with a pressure input and a vacuum output, managed the pressure of the balloons to simulate an human respiration cycle, pushing or pulling the air inside the balloons.

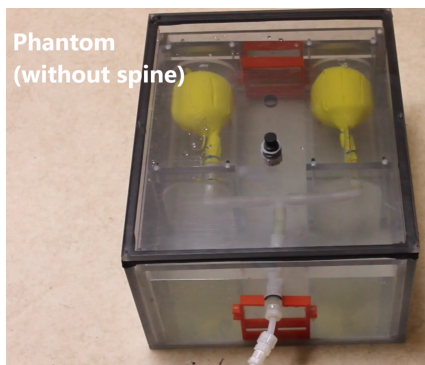


Figure 3.10: Pneumatic phantom for mimicking respiration-induced artifacts in spinal MRI developed by the Institute of Biomedical Engineering at Polytechnique Montreal [47]

4 Pahl and Beitz design process

This section is dedicated to the presentation of the four last steps in the design process, which are :

- establishment of the functional analysis;
- search for solutions;
- choosing the solution;
- presentation of the detailed final solution.

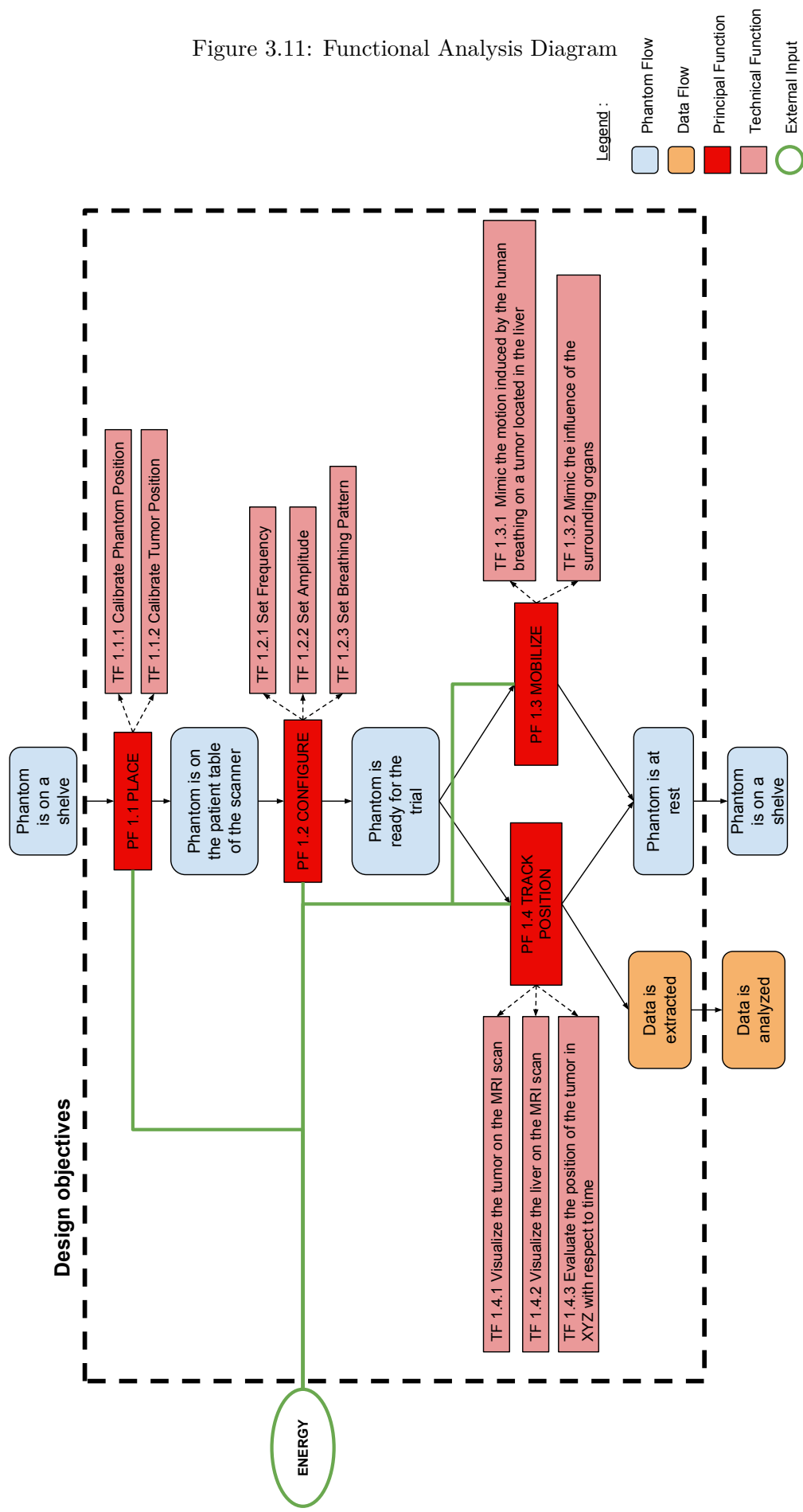
4.1 Functional analysis

As mentioned before, the next step in the design process is to identify the technical functions needed to fulfil the specifications. To do that we establish a functional analysis diagram that can be seen in Figure 3.11 and which defines the goal and the scope of our design in the environment where our device will be used.

It consists in the graphical representation of a succession of actions (represented in the soft edge squares) and states (in the hard edge squares) connected by the physical flow of the phantom (in blue) and the flow of the data extracted from the device (in orange).

Every action will match with one of the principal functions (the "PF" in red) and by detailing the functions, all the independent technical functions are obtained (the "TF" in pink). These functions serve as a basis for the rest of the search for solutions.

Figure 3.11: Functional Analysis Diagram



4.2 Search for solutions

Once the 10 different functions have been identified and with the existing solutions in mind, the goal was to come up with as many ideas to fulfil these functions as possible. Gathered under the form of a morphological graph, it can be seen in the Appendix C. In this part of the process, constraints such as the feasibility, the MRI compatibility or the manufacturing price should not be taken into account. The main purpose is to generate concept of ideas that could work. Drawing is crucial for understanding the concepts of the expressed solutions, as shown below with the line of the morphological graph concerning the mobilization function (Figure 3.12).

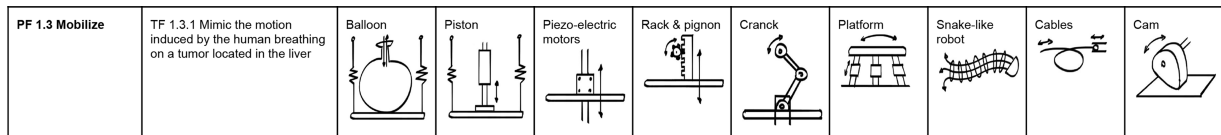


Figure 3.12: Morphological solutions for the mobilize function

4.3 Choosing the solution

To be able to assess our conceptual ideas, the first thing to do is to agree on a list of criteria. Below, we ranked all these criteria from the most important to the least. This is why a decreasing weight from 7 to 1 credits has been given to each criterion.

- Feasibility (6 credits) : Maturity of the technology, MRI safety and compatibility.
- Price (5 credits): Cost of the manufacturing components as well as the cost of use and maintenance.
- Accurate measurements (4 credits) : Precision of the tracking system.
- Human resemblance (3 credits)
- Accurate movements (2 credits)
- Modularity (1 credit)

Generally, choosing the best solution for each function does not identify the best overall solution because a combination of several less attractive solutions may ultimately be more suitable. However, as they are completely independent from the rest of the solution, some of the technical functions were assessed individually and the best options were chosen:

- For calibration of the Position of the phantom : Alignment Lights.
In order to place the phantom correctly in the MRI enclosure, it is possible to project a light cross on the bench. From then on, simply align this cross with a cross drawn on the phantom would be enough to adjust its position.
- For the calibration of the position of the tumor : Fixed Beacons
The exact position of the tumor before motion can be established by comparing its position with the known position of certain fixed marks on the MRI image.

For the rest, four different combinations were created (Figure 3.13).

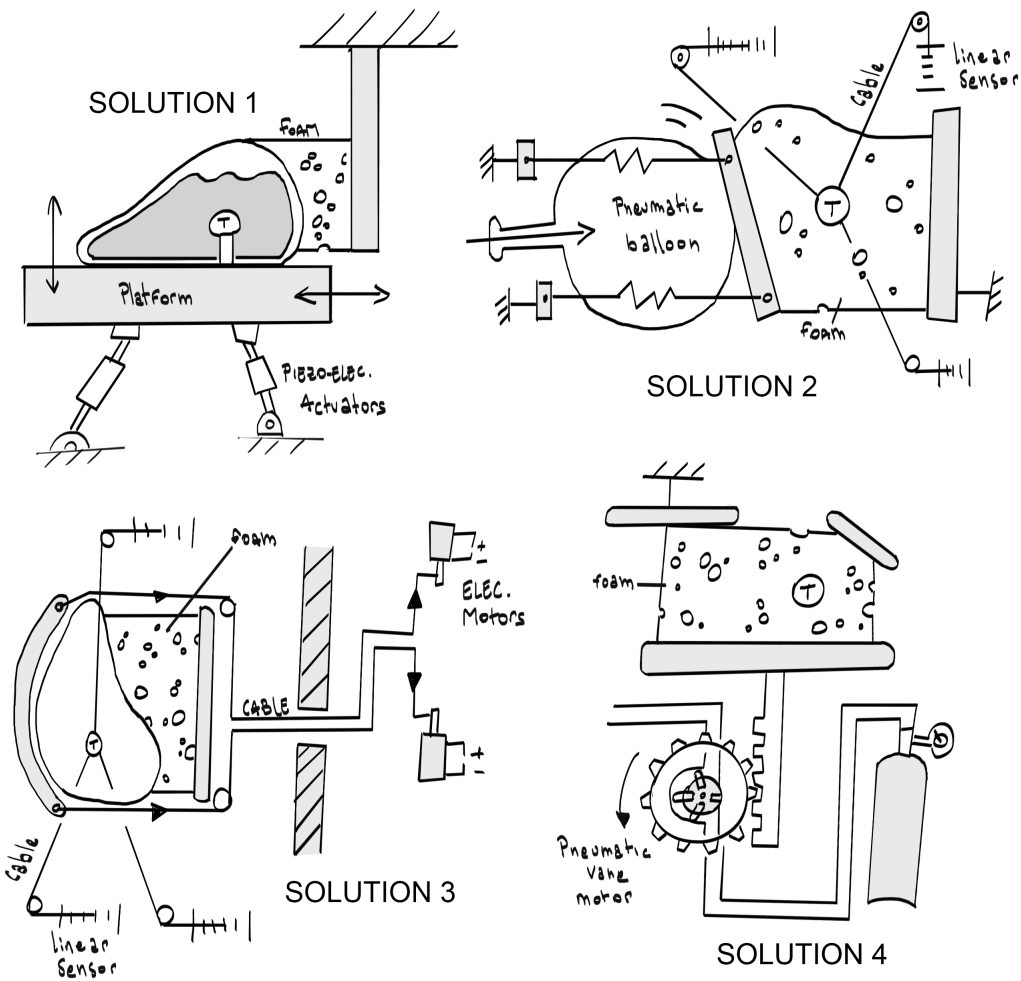


Figure 3.13: Combinations of solutions

Solution 1 : A false non-rigid organ is placed on a movable platform with 2 degrees of freedom. The tumor is attached to the platform in order to know its position as a function of the movement performed by the actuators. The influence of the surrounding bodies is simulated by a foam/gel independent from the platform.

Solution 2 : A pneumatic balloon compresses a series of gels and foams representing the abdominal organs. These are inscribed between two plates, one fixed and the other is connected to spring or elastic whose stiffness is known. The tumor is connected to three rigid cables and its position is defined by triangulation with their displacement.

Solution 3 : Here the movement is provided by one or more electric motors located outside the room. These would generate the breathing motion by winding or unwinding cables that would be connected to the false diaphragm. The organs would also be represented as gel/foam and the tracking would be the same system as shown in the previous solution.

Solution 4 : A pneumatic vane motor connected to a rack linearly mobilizes a plate representing the diaphragm. The bodies that are interesting to visualize would still be represented in foam, but the influence of the other organs would be mimicked by plates or other rigid obstacles. In this case, we considered that the movement would be sufficiently predictable to know the position of the tumor at all times.

Concerning the evaluation process, solution 2 was chosen as the reference solution. For each criterion, the other combinations have either been considered better (represented by a plus in the table below) or worse (represented by a minus). Then the weights of the criteria were added or subtracted to obtain the final score for each solution.

	Solution 1	Solution 2	Solution 3	Solution 4
Feasibility (6)	-	0	0	0
Price (5)	-	0	-	-
Accurate measurements (4)	+	0	0	+
Human resemblance (3)	-	0	-	-
Accurate movements (2)	+	0	+	+
Modularity (1)	+	0	+	0
Total	-7	0	-5	-2

Table 3.1: Assessment of the solutions

Following the results of the table, we opted for the reference solution. However, after several discussions with technicians, mechanical triangulation was replaced by camera tracking. Although easier to set up, it requires the transparency of all the obstacles between the lens and the tumor.

4.4 Final Solution

At the end of this process, the final design has been identified. Yet the latter still had to be detailed in order to obtain a convincing prototype idea. The conceptual phantom consists of a rectangular box made of see-through Plexiglas, separated in two parts by an elastic membrane. The first part (in white in Figure 3.14 and to the left of the box) is completely sealed to be able to house compressed air. The entire pneumatic regulation system is placed outside the MRI room. The organs (a liver, a stomach and a pancreas) are placed in the second part of the phantom (in grey and to the right of the box). These are mainly made of gelatin, as well as products to alter the MRI contrast. A fake tumor is placed inside the liver. The latter shall be represented by a coloured ball or even made of a fluorescent material in order to enhance the camera imaging contrast. The rest of the compartment is filled with water and the organs are bound with each other using glue or velcro. Two cameras are placed above and beside the phantom to respectively track the movement in the coronal and sagittal plane.

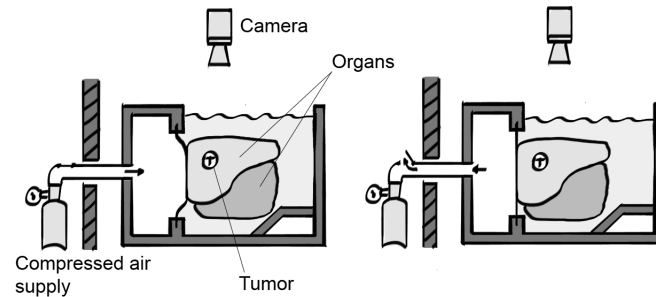


Figure 3.14: Lateral view of final design

The compressed air injected into the left part of the phantom will inflate the elastic membrane, which will mobilize the adjacent organs (See Figure 3.14). The geometry of the box mimics the influence of the vertebral column and the pelvis. Moreover, the variation of the water level reproduces the swelling of the belly. Afterwards, the air is breathed out to return to the initial position to be able to repeat this cycle at will. The inlet and outlet of the pressurized air is controlled by an electro-valve.

Chapter 4

Technical characteristics

Once the concept was set, we moved on to the practical realization phase. A diagram of the final prototype can be seen in the Figure 4.1. The electric cables are represented in black and the pneumatic system in blue. Overall, the device looks pretty much like the original idea. The phantom is a box separated in two parts by an elastic membrane. On one side, the surrogate organs, made out of *CAGN* gel¹ are immersed in water. These organ-like gels are attached to each other and to the membrane with rubber bands. On the other side, compressed air is injected into the second part of the box, causing the membrane to inflate and deflate. The compressed air flow is regulated by an electro-regulator controlled by an electrical signal generated by the digital-analog converter (NI MyDAQ™, National Instruments Corp., Austin, Texas) . The input signal of the MyDAQ™ is sent by a LabVIEW™-based computer software (NI ELVISmx, National Instruments Corp., Austin, Texas). The supply and output of the valve are connected to the compressed air and negative pressure of the hospital network respectively. A MRI-compatible eye-tracking camera connected to a computer tracks the movement of the organs from the inside of the machine enclosure.

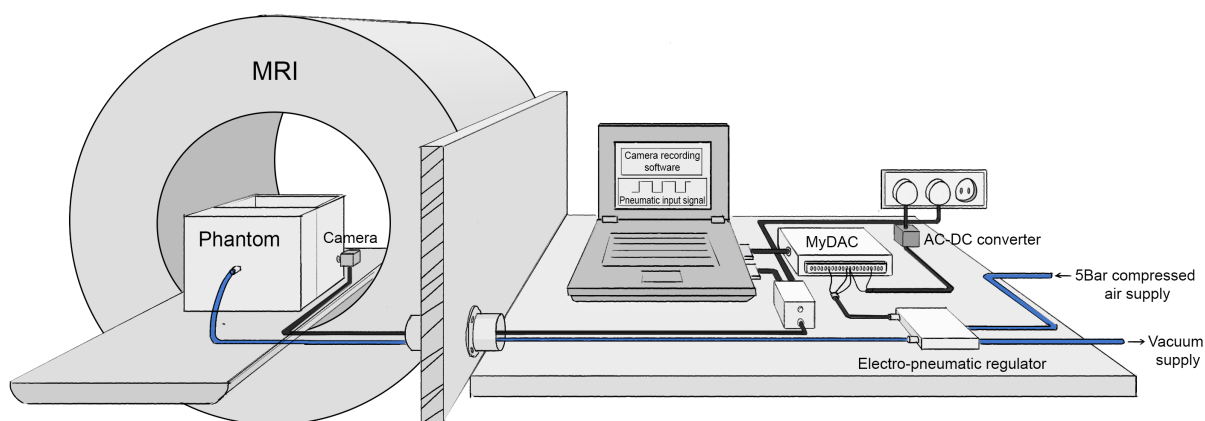


Figure 4.1: Schematic representation of our solution

The fields covered by the construction of this prototype are multidisciplinary, including mechanics, pneumatics, computer sciences, electronics and material sciences. This chapter reviews

¹*CAGN* gel is a gadolinium-agarose based water gel reinforced by carrageenan and containing sodium chloride first described by Kato et al. [48]

the components of the prototype one by one, detailing the computation, the manufacturing or the implementation method of each of these parts.

1 The box

In the final solution, a rigid box of rectangular section represents the human torso, containing the upper-abdominal organs and the diaphragm. The geometry of the box has been derived from the MR images of the trunk of a human body, transmitted by Damien Dasnoy-Sumell. The overall dimensions of the boxes are 200 mm in height, 260mm in length and 210mm in width. Complete blueprints can be found in Appendix D. On the images of the sagittal plane of a human being (Figure 4.2), the reader can notice that the abdominal (left) and the dorsal (right) walls are slightly inclined. On the one side, this inclination is due to the presence of the vertebral column at the back of the body, which reaches a height of 38mm at the end of the pancreas. On the other side, the abdomen is stretchable and expands by about 10mm (Figure 4.2) during the breathing cycle. To simulate these phenomena, a wedge of increasing height represents the spinal column at the bottom of the liquid-filled part and the water level can be raised freely to mimic to the swelling of the abdomen. This geometry induces a 2D motion of the organ-like gels during the activation of the phantom.

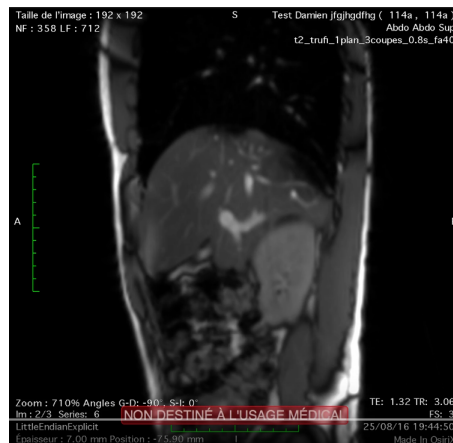


Figure 4.2: MR sagittal view of the torso of a human being

During the design process, several implementations of the box were considered (Figure 4.3). The first one consisted of a grey PVC cylinder separated by an elastic membrane stretched by compressed air. This option has been ruled out for several reasons. First, the cylindrical shape could induce distortions of the image recorded on the camera external to the tube. The processing of the images to recover the exact geometries of the inside of the phantom would be more complex than in the rectangular case. Secondly, PVC is a completely opaque material. To be able to combine the camera-tracking system with this design, an opening in the cylinder would have been necessary. This opening could have only been performed on the top of the cylinder such that the tracking in the sagittal plane would not be possible. Moreover, we were afraid that the opacity of the walls would make the inside too dark. In this case it would not be possible to differentiate the contrast of the tumor from the rest of the organs without the use of an additional light, such as a LED for example, which could potentially disturb the magnetic field of the scanner. It is for this reason that transparent Plexiglas Vivak® (10mm thick) was chosen for the manufacture of the box. In other options, different systems for the motion actuation, as in solutions 2 and 3 (Figure 4.3), were considered. These consist of a rigid plate using a pneumatic piston or of an inflated balloon respectively. Yet, the plate has to be directed by a linear guide, unfortunately the restriction of the use of ferromagnetic material did not allow to call on slides

already existing on the market. In addition, problems of leak-tightness of the balloon and the piston led to the choice of a hybrid solution of the three previous ones.

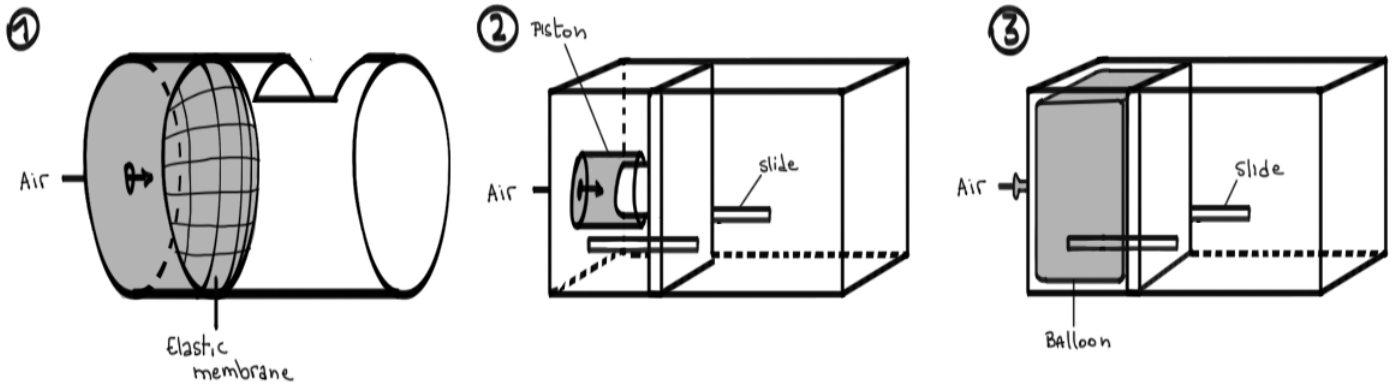


Figure 4.3: Different designs for the boxes

Concerning the construction of the box, we called on a company outside of the university (Plastiservice Group ²) in order to ensure the correct sealing of the box.

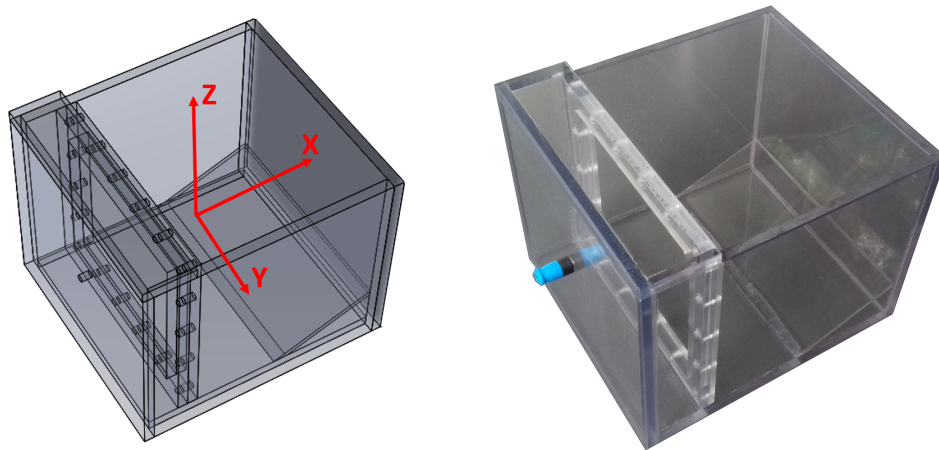


Figure 4.4: SolidWorks representation of the box (left) next to a picture of the actual box (right). A reference frame (X,Y,Z) with respect to the box is introduced on the left picture.

2 The membrane

In our design, the membrane is supposed to represent the diaphragm. However, in a real human body, it is concave from the point of view of the rib cage. On Figure 4.5, two MR scans of the sagittal plane of an human torso are represented. In grey : at the end of the expiration phase. In red : at the end of the inspiration phase. In green : the area travelled by the diaphragm during a normal respiration cycle.

Since the positive pressure in the lab and at the hospital can provide a bigger pressure potential than vacuum, a convex membrane had to be implemented. As mentioned previously, the amplitude reached when an adult patient breathes normally is 2cm [49] (Figure 4.5).

²<http://www.plastiservice.com/fr/accueil>

Regarding the material used for the membrane, two lined up 1.5mm membranes of Firestone GeoGard™ EPDM 1.5³ were used. First, a 1mm Wacker Silicone Elastosil® membrane molded by Xavier Bollen was tested. However, tests showed that it was not elastic enough and it did not have a return force strong enough to expel the air out of the box with the negative pressure available.

For the manufacturing, the three aspects kept in mind were, firstly, to ensure water and air tightness between the two parts of the box, secondly, to be able to change the membrane and, finally, to remain MRI safe. To do this, the membrane is pinched between two 1cm thick Vivak frames. These two frames are attached to each other using 18 M6 nylon screws (Figure 4.6). These screws pass through holes previously made in the rubber sheet, which thus also serves as a seal.

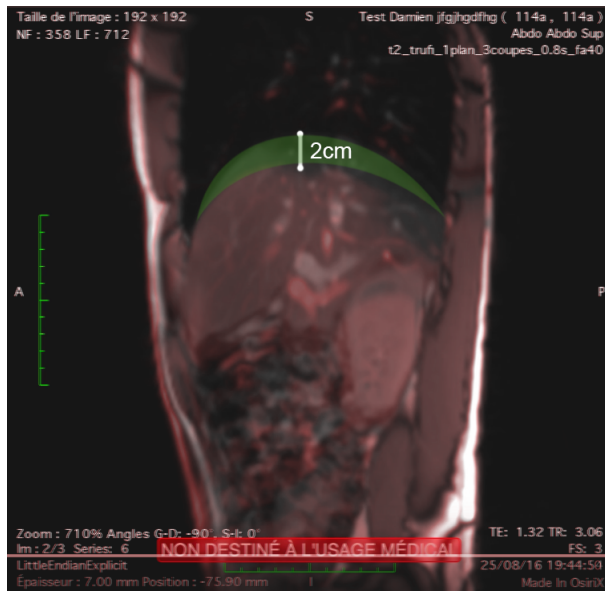


Figure 4.5: Comparaison of two sagittal scans of the torso. In grey: at the end of the expiration. In red: at the end of the inspiration



Figure 4.6: Picture of the clamping system

3 Electro-pneumatic system

The Figure 4.7 illustrates the electro-pneumatic circuit that handles the motion of the membrane and the organs. The purpose of this circuit is to control the pressure inside the air compartment of the phantom, which is separated from the water compartment by the flexible membrane. The increase or decrease of the pressure inside this part will inflate or deflate the membrane providing a motion that represents the human diaphragm moving during the respiratory cycle.

³A 1.5mm black polymeric geomembrane produced by Firestone Building Products

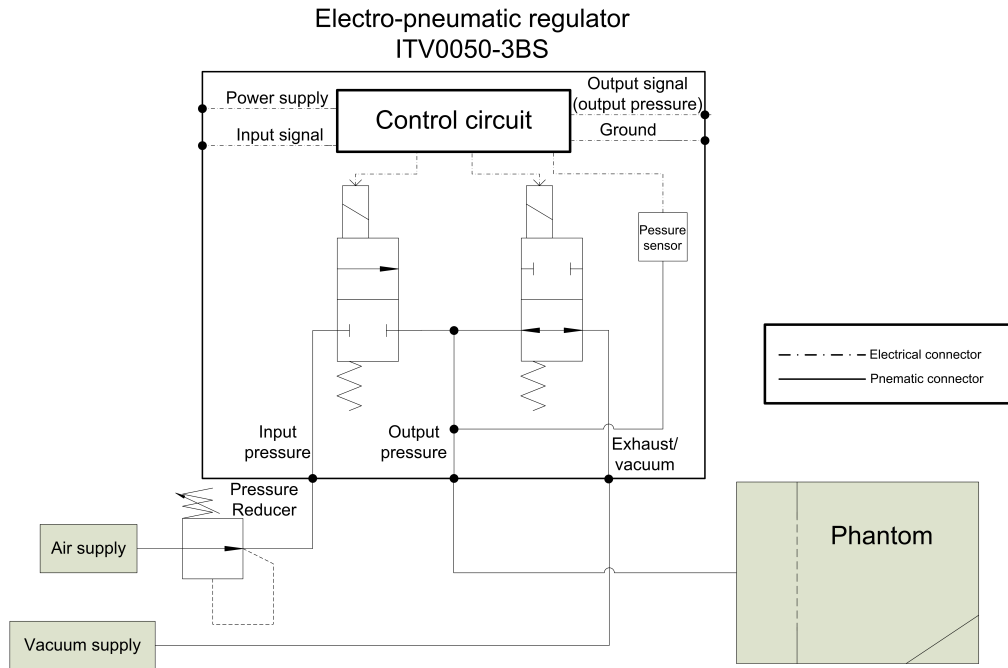


Figure 4.7: Schematic of the electro-pneumatic circuit of the phantom that is used to inflate and deflate the membrane reproducing the motion of the diaphragm.

The main elements on the electro-pneumatic diagram are :

- **The air supply** with 5 bar of pressure relative to atmospheric pressure;
- **the vacuum supply** with -0.8 bar of pressure relative to atmospheric pressure;
- **the electro-pneumatic regulator** ITV0050-3BS [50] connected to the pressure reducer as input, to the vacuum as exhaust and to the phantom as output;
- **the pressure reducer** appears in the diagrams but it is not needed because the input pressure does not exceed 5 bar ; it is a security measure to limit the input pressure of the regulator that can not exceed 9 bar .

The regulator contains two solenoid valves – connecting or disconnecting the positive or negative pressure to the phantom – a pressure sensor and a control circuit. This logical circuit activates or deactivates the solenoids of the valves to maintain an output pressure proportional to the electrical input signal. Therefore, the motion of the membrane can be controlled by an electrical signal.

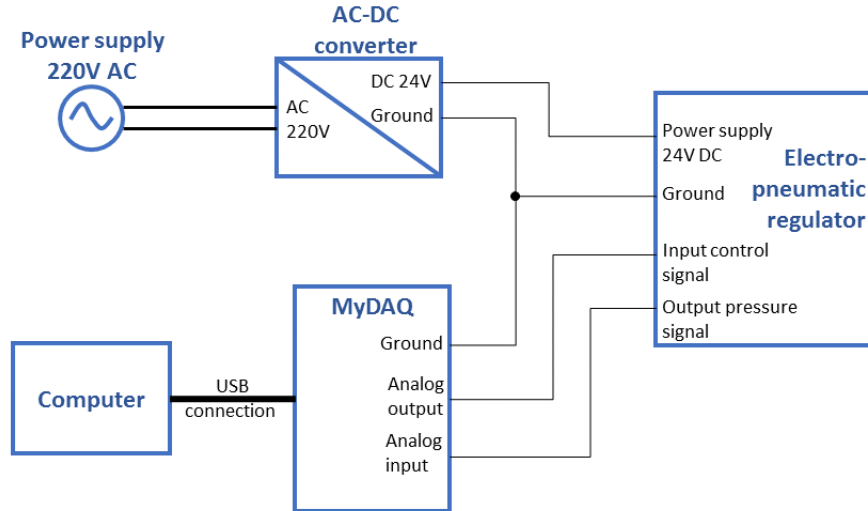


Figure 4.8: Schematic of the electrical circuit to supply the power and control the electro-pneumatic regulator

In order to create the electrical signal generating a motion that corresponds to the requirements (see Chapter 3, Section 2), an electrical setup is needed. The schematics of this latter are visible on the Figure 4.8. The upper part of the diagram is used for the power supply of the regulator which needs continuous 24V and 0.12A. So, an AC-DC converter is used to convert the 220V, 50Hz, 16A from the hospital electrical network to 24V DC (and maximum 0.17A, which is enough).

The lower part of the diagram is composed of a computer connected to a digital-analog converter (NI MyDAQ™ [51], National Instruments, Austin, Texas), itself connected to the input/output of the electro-pneumatic regulator. The MyDAQ™ allows to generate an arbitrary waveform with a simple user interface on the computer (NI ELVISmx™, National Instruments, Austin, Texas) for the input control signal of the regulator and to read its analog output that is proportional to the pressure inside the phantom.

So the entire electro-pneumatic system generates a programmable motion inside the phantom that is controlled by a user interface on the computer.

The Figure 4.9 shows the part of this user interface used to create the electrical signal to control the electro-pneumatic valve. Many functions can be implemented : there is a library of basic functions (as the square one in the picture), a possibility to encode the mathematical expression of the function and even to draw it by hand.

The Figure 4.10 is a screen capture of the LabVIEW™ (NI LabVIEW™, National Instruments, Austin, Texas) user interface of the oscilloscope integrated inside the MyDAQ™. It is used to view the output signal of the electro-pneumatic regulator that is proportional to the pressure inside the air compartment of the phantom.

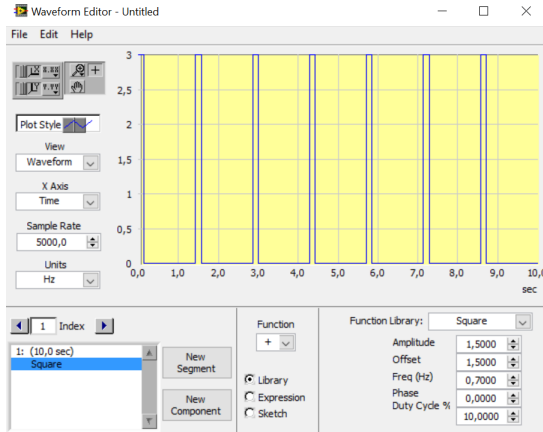


Figure 4.9: User interface of the NI ELVISmx software on the computer to create the electrical signal to control the electro-pneumatic valve

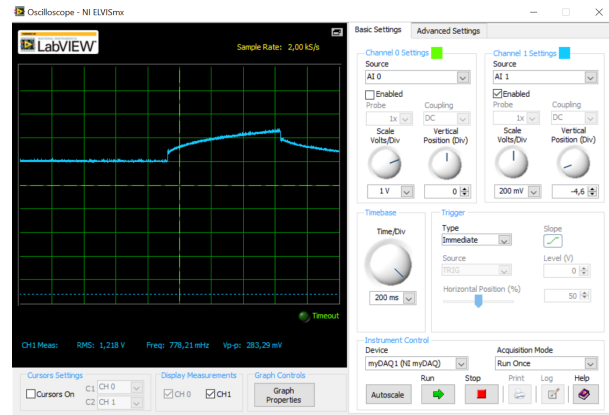


Figure 4.10: Screen capture of the NI LabVIEW user interface of the oscilloscope integrated inside the MyDAQ™ that shows the output signal of the electro-pneumatic valve

The Figure 4.11 presents the respiratory system of the phantom developed by the Institute of Biomedical Engineering at Polytechnique Montreal [47] (recall Chapter 3, Section 3). With the agreement of the team of Polytechnique Montréal, this system has been reproduced and adapted to create the motion system of our phantom.

Inflation system

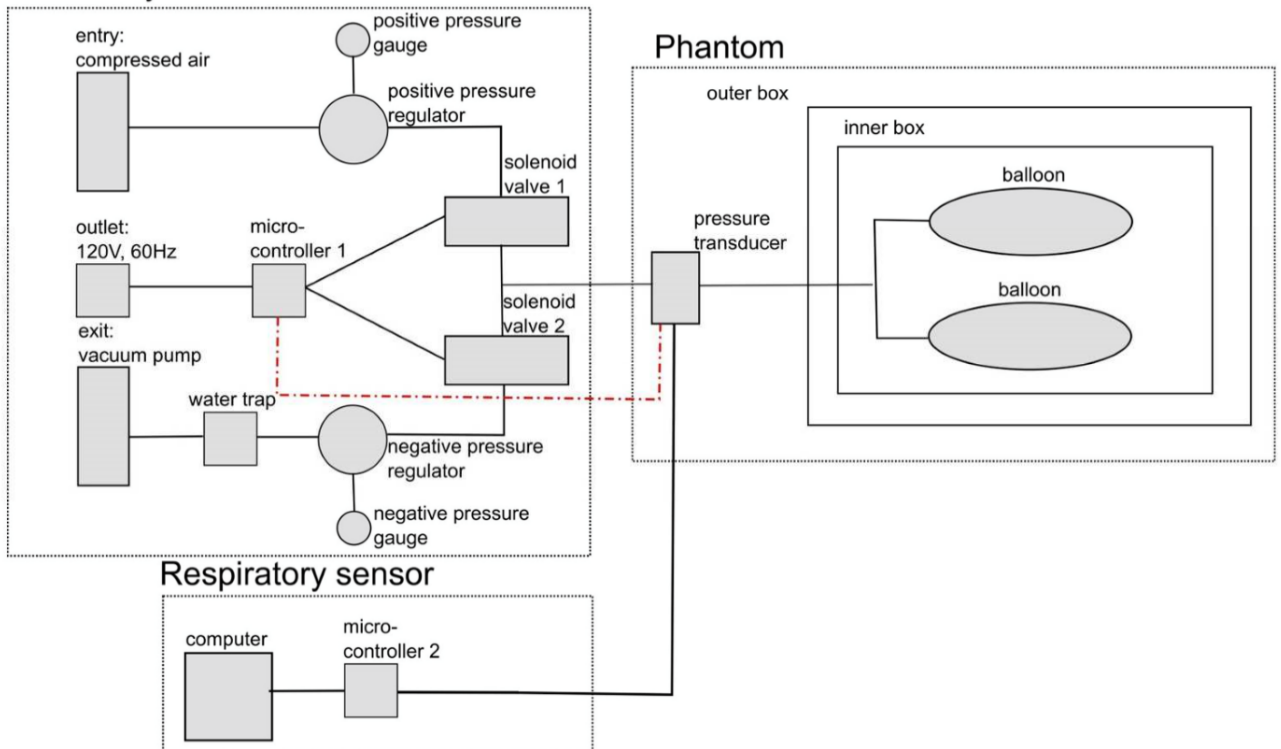


Figure 4.11: Schematic of the artificial respiratory system of the phantom of Polytechnique Montréal [47]

The comparison between Figures 4.8, 4.7 and 4.11 shows the similarities and the differences between our phantom and the one of Polytechnique Montréal.

The electro-pneumatic regulator has made it possible to assemble in one single element the microcontroller, the two electro-pneumatic valves and the pressure sensor.

However, it needs a supply of 24V DC which is provided by an AC-DC converter and the input control signal and output pressure signal are managed by a MyDAQ™, linked to a computer for the user interface.

The rest of the circuit and its logic is quite the same in both phantoms, with a positive and a negative pressure that are connected to the part of the phantom to inflate or deflate via two solenoid valves.

4 Tissue surrogates

The phantom contains four tissue-like gels. Three gels mimic a specific organ of the upper-abdominal part of the human body – a liver, a stomach and a pancreas – and the last one represents a hepatocellular carcinoma (HCC)⁴.



Figure 4.12: Liver with tumor, stomach and pancreas : Top view (left) and front view (right) of the phantom device

The human tissue surrogates presented on Figure 4.12 are committed to a faithful representation of the human body and particular attention is given to their appearance on MR images. In agreement with the specifications related to the entire phantom device (see Chapter 3, Section 2) and on the basis of the recommendations stated in the literature [54][55][56], the objectives the tissue surrogates were asked to meet were limited to the following ones (order does not matter) :

- Similar shapes than those of the human organs
- "*Shape retaining strength without reinforcement*" (Yoshimura et al., 2003)(Seiichiro et al., 2008)
- Transparency for the visual tracking of the tumor
- "*Equivalent relaxation times and electrical conductivity to human organs*" (Yoshimura et al., 2003)(Seiichiro et al., 2008)

⁴Hepatocellular carcinoma (HCC) are the most common solid liver lesions in a cirrhotic liver [52] and the most common primary liver tumors worldwide [53]

- "Uniform relaxation times and electrical conductivity over the entire tissues" (Yoshimura et al., 2003)(Seiichiro et al., 2008)
- Exhibit the above characteristics at room temperature
- Cheap components and easy preparation
- Long term quality

The relaxation times T1 and T2 (detailed in Chapter 2, Section 4), proper to each tissue of the human body, are essential for the image reconstruction. Indeed, the intensity of the acquired signal is dependent on the T1- and the T2-weighting of the imaging sequence. Moreover, the dielectric properties of the human tissues are important to explain the heat increase and the current loops that may occur in the MR scanner during the imaging. In parallel to these intrinsic properties of the organs, the shape of the tissue surrogates have to help the user of the phantom to recognize easily each component on the images and to compare them with real models. These requirements for human tissue-like substitutes were to be combined with the proposed visual tracking solution (see Chapter 3, Section 4.4, and the technical details in Section 7 of this chapter) as well as with the limitations and the expectations regarding the budget, the quality and our technical skills.

In general, two types of phantoms are used in the MRI environment : aqueous solutions and gel materials.

Aqueous solutions contain paramagnetic ions such as $CuSO_4$, $NiCl_2$, $MnCl_2$, or $GdCl_3$. They are intended for MRI equipment calibration and check-up because of the homogeneity of the relaxation times throughout the solution and their stability over time. However, liquid phantoms do not retain in the shape of organs without a container. Moreover, with liquid phantoms, T1 and T2 relaxation times can not be handled independently from each other, which prevents from mimicking properly the relaxation times of human organs. On top of these drawbacks, the aqueous solutions are prone to flow and motion artifacts [37]. These aspects may be corrected by the use of gel materials composed of T1- and T2-modifiers [45][46][54][55][48]. The semi-solid behavior of gels restricts a part of the water to move freely under the influence of the magnetic field. Several gelling agents have been tested in the purpose of MR experiments to modify the T2 values of the phantom independently from the T1 values, affected by the paramagnetic ions. These phantoms include polysaccharide gels (agarose, agar), protein gels (gelatin), polyvinyl alcohol (PVA) gels, polyacrilamide gels and silicone gels [55][48][57]. However, as mentioned by Seiichiro et al. "*preparations of PVA, polyacrylamide, or silicone gels is time-consuming, and costly, and their sizes and shapes cannot be easily changed*" [55]. Polysaccharide and protein gels are less difficult to produce and are very cheap since their components are often used in the food industry. However, their density may be too low if long T2 values are required, which can affect the strength of their shape.

As a result of our research around the possibilities for the human tissue surrogates, we chose to follow the model derived from Kato et al.'s research on the implementation of agarose and gadolinium gels reinforced by carrageenan and containing sodium chloride to reproduce human organs at 1.5T and 3.0T [48][58]. This type of gel is called the *CAGN phantom*.

Relaxation times of human organs

As stated previously, the relaxation times, T1 and T2, are specific to each human tissue. They have an impact on the contrast of the reconstructed image by affecting the intensity of the MR signal.

To be able to reproduce the same intensities as real organs on MR images, the gels in the phantom have to mimic the relaxation times of these organs. T1 and T2 values depend on the amount of protons in motion in the tissue and also on the Larmor frequency, the frequency at which the transverse magnetization rotates. This frequency is directly proportional to the magnetic field $\mathbf{B}_0$ and is equivalent to 42.58MHz at 1.0T, as stated in Appendix A. The T1 and T2 values of tissues are derived from T1/T2 mapping images respectively.

In the frame of this master thesis, the approximate T1 and T2 values, at 3.0T, of the liver, a tumor in the liver (hepatocellular carcinoma), the stomach and the pancreas had to be collected in the literature. The intensity of the magnetic field is imposed by the MRI scanner used for the tests at the Cliniques Universitaires Saint-Luc (CUSL). Several papers from the Faculty of Health Science of the Okayama University Medical School (Japan) have listed these values at different Larmor frequencies from their experiments and from previous publications [48][58][59]. Table 4.1 gathers the selected values to be reproduced.

	Liver	HCC	Stomach	Pancreas
T1 (ms)	812	1217	1328	725
T2 (ms)	42	74	61	43

Table 4.1: Relaxation times of the organs to be mimicked, at 3.0T [58][59]

The reader should pay attention to the following points concerning the values listed in Table 4.1.

- The T1 and T2 values are the mean relaxation times of an entire tissue. These values are highly susceptible to change throughout the tissue, due to inhomogeneities of the tissue and of the magnetic field. Moreover, these values may be different from one patient to another, due to variability of the human nature.
- The relaxation times of the tumor are approximated on the basis of the values corresponding to 1.5T from Kato et al.'s (2005) [48] paper. They are adapted following the findings of de Bazelaire (2004) [59]. The author states the T1 values increase by 21% from 1.5T to 3.0T and the T2 values decrease by 8% for the liver.
- The values given for the stomach correspond actually to the values of the spleen because they were not listed in the literature. Indeed, according to M. D. Alexandre Mosseray, as the stomach is a hollow organ with variable fillings, the T1 and T2 spectrum is uneven.
- As a general statement, the order of magnitude of the T1 relaxation of a human tissue is ten times longer than the T2 relaxation [48].

Dielectric properties of human organs

Radiofrequency radiations have a thermogenic effect during MR procedures. A great amount of the radiofrequency power is transformed into heat within the tissues due to resistive losses [60]. There is a "significant risk", according to the US Food and Drug Administration (FDA), when the specific absorption rate (SAR) is greater than 4W/kg for 15 minutes (more restrictive SAR are prescribed for sensitive parts of the body) [61]. This effect has to be considered for continuous imaging of the patient.

To integrate the resistive behavior of the human tissues in the gel phantoms, the dielectric properties of the organs were inspected. These properties are defined as the relative permittivity ϵ' (F/m) and the conductivity σ (S/m), which depend on the frequency of the electromagnetic waves radiating the tissue.

$$\epsilon' = C/K \quad \sigma = G\epsilon_0/K$$

where C and G are the capacitance and the conductance of the probe evaluating the dielectric properties, and K is the capacitance in air of the probe ϵ_0 is the permittivity of vacuum.

The relative permittivity is a measure of the resistance of the material to the generation of an electric flux. It varies with the increasing frequency due to the following mechanisms : ionic diffusion around the cellular membrane, polarization of the cellular membrane and, finally, polarization of the water molecules. Conductivity is related to the ionic content of the tissue and to the mobility of these ions. It indicates the ability of the material to conduct electricity. The characterization of the dielectric properties of body tissues have been covered by Gabriel C. [62] in a re-evaluation of the previous measurements stated in the literature [63][64][65].

At frequencies under 100Hz, biological materials act mostly as resistances [62]. The values vary widely when the range of frequencies exceeds this threshold. The dielectric properties can be easily determined for each human tissue and for a broad variety of frequencies thanks to the application developed by the Italian National Research Council (INRC) and available on their website⁵. The estimated permittivity and conductivity of the liver, stomach and pancreas were computed at the Larmor frequencies relative to 1.5T and 3.0T respectively, i.e. 63.87MHz and 127.74MHz [66][67]. Since the dielectric properties do not affect the relaxation times of polyacrylamide gels [68], such as the ones produced in the context of this master thesis, the dielectric properties of the stomach correspond to the actual properties of the stomach and not to the ones of the spleen as it was decided for the T1 and T2 values of this tissue surrogate.

	Liver	HCC	Stomach	Pancreas
ϵ' (F/m)	64.286	/	74.917	66.799
σ (S/m)	0.51068	/	0.91269	0.80407

Table 4.2: Dielectric properties (relative permittivity ϵ' and conductivity σ) of the organs to be mimicked, at 3.0T [66][67]

Gel components

The literature advises various components to independently modulate the relaxation times and other properties of gel phantoms. The searchers of the Faculty of Health Science of the Okayama University Medical School (Japan) have proposed a gel composition named "*CAGN phantom*" displaying the dielectric properties and the magnetic properties of human tissues [48]. The gel material is essentially composed of carrageenan, agarose, gadolinium, sodium chloride and distilled water. In addition to these main components, sodium azide completes the preparation. All of these components play a specific role in the gel phantom. A summary of the components and their supplier is at the disposal of the reader in Appendix E.

⁵<http://niremf.ifac.cnr.it/tissprop/htmlclie/htmlclie.php>

The different compounds and their impact on the properties of the final gels are detailed below.

- **Carrageenan (C)** – the gelling agent. Carrageenan is extracted from *Rhodophyceae* (red algae). It is commonly used in the food industry as an additive to thicken, gel, stabilize or emulsify the preparation [69]. This agent "is a hydrocolloid consisting mainly of the potassium, sodium, magnesium, and calcium sulphate esters of galactose and 3,6-anhydrogalactose copolymers" (CP Kelco, J.M. HUBER Corp.) [70]. It is a large molecule with many structural possibilities but, in general, it can be characterized by the three main types : kappa (κ), iota (ι) and lambda (λ) carrageenan. Carrageenan is insoluble in ethanol and soluble in water at temperatures of 70°C and higher. "In ionic solutions, κ - and ι -carrageenans self-associate into helical structures that form rigid or flexible gels, respectively. λ -carrageenans do not form helices and are non-gelling" (Merck KGaA Corp.) [71]. "It disperses in water more readily if first moistened with alcohol, glycerol, or a saturated solution of glucose or sucrose in water" [69]. "When dissolved by heating, followed by cooling below certain temperatures, kappa and iota carrageenans form thermoreversible water gels in a concentration as low as 0.5%, provided gelling cations are present. A gel has some properties of a solid and some of a liquid. Thus, it keeps its shape when tipped out of a container and yet retains the vapour pressure and conductivity of the liquid from which it is made." [70]. Carrageenan gel strength comes close to 1200g/cm² for concentrations of [C] = 3%.

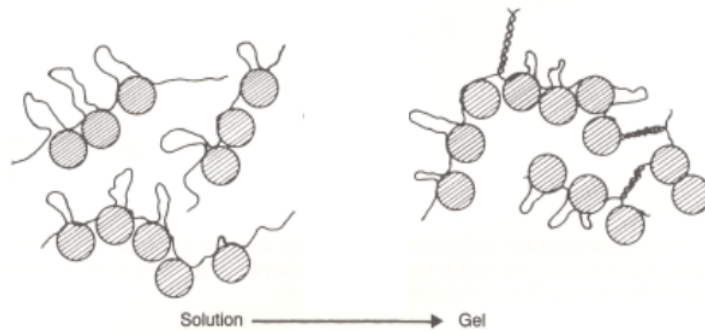


Figure 4.13: Gelling mechanism of carrageenan at the molecular level [70]

- **Agarose (A)** – the T2-modifier. Agarose is also a polysaccharide material derived from *Rhodophyceae*, as carrageenan. It is the gelling component of agar (or agar-agar), widely used in the food industry. Agarose is insoluble in cold water but it dissolves at high temperatures approaching water's boiling temperature (90°-95°C). Its gelling point is at 35°C [71]. Unlike carrageenan, the gelation of agarose in an aqueous media affects very few cations and proteins [72]. However, the gel mechanism is still the same (see Fig. 4.13), except that helices are left-handed in agarose, due to 3,6-anhydro-L-galactose, whereas they are right-handed in κ and ι carrageenan, because of the 3,6-anhydro-D-galactose [72]. The produced gels are very stable over time and are clear for low concentrations of agarose (<1.5%). Their gel strength reaches up to 975g/cm² for concentrations of [A] = 1.35%.
- **Gadolinium (G)** – the T1-modifier. Gadolinium is a chemical element (Z=64) used as a paramagnetic contrast agent with effect on the longitudinal relaxation (T1) of the hydrogen nuclei, leading to a hyper signal on T1-weighted images [31]. "Gadolinium contrast agents are widely used in clinical practice to enhance tumors, the blood pool, and myocardial infarcts, to list a few applications" (Jacques et al., 2010) [73]. Gadolinium is toxic in its free state and is administrated in chelate⁶ form. "At weak concentration, the T2 effect of

⁶"(chemistry) a cyclic compound in which a metal atom is bonded to at least two other atoms" [74]

Gadolinium chelates is negligible compared to the T1 effects" (IMAIOS) [31]. The effect of Gadolinium on the relaxation times is characterized by its relaxivity r_1 and r_2 :

$$\frac{1}{T_i} = \frac{1}{T_i^0} + r_i[G] \quad i = 1, 2 \quad (4.1)$$

with $\frac{1}{T_i^0}$, the inherent relaxation rate and $[G]$, the concentration of contrast agent. The relaxivity of Gadolinium is dependent on the magnetic field applied and on the temperature. The contrast agent induces the nuclear relaxation by creating a fluctuating magnetic field, related to tumbling motion of the complex in the solution, which in turn induces the relaxation of the hydrogen nuclei. "*The fluctuating field can also be a result of the electrons in the Gd_3^+ ion undergoing excitation and relaxation*" (Jacques et al., 2010) [73].

- **Sodium Chloride (N)** – the electrical conductivity modifier. Electrical currents in the human body are the result of ionic displacements. Among the ions responsible of these currents, Na^+ and Cl^- , derived from ionized sodium chloride (NaCl), are essential. Sodium chloride is abundant on planet Earth and is essentially produced by solar evaporation of sea water and rock mining [75]. It dissolves in water at room temperature due to the high polarity of water molecules. Once dissolved, the ions are dispersed in the solution and contribute to its dielectric properties.
- **Sodium Azide** – the antiseptic. Since a large amount of water molecules are still free in the structures produced in the context of this master thesis, bacterias may nest inside the gels. Sodium azide (NaN_3) is a highly toxic inorganic compound which is used as an antiseptic [48] to avoid harvesting germs in the gel preparations. Sodium azide is an ionic solid with two possible crystal configurations : rhombohedral and hexagonal [76]. It is highly soluble in water.
- **Water** – the hydrogen source.

The searchers of the Faculty of Health Science of the Okayama University Medical School (Japan) have published the results concerning the influence of the main components of the *CAGN phantom* on the T1 and T2 values of this gel at 1.5T and 3.0T [48][58].

It has been demonstrated that the *CAGN phantom* provided surrogates with relaxation times of a broad variety of human tissues; from different brain tissues to bone marrow, muscle, fat, and so on [48][58]. The influence of agarose, gadolinium and sodium chloride, on the relaxation times of the gels has also been assessed. The experimental results showed how very little influence had gadolinium and agarose on T2 and T1 values respectively, and how sodium chloride affected these two values. Table 4.3 summarizes these conclusions and Figure 4.14 illustrates the variations in T1 and T2 following variations in G and A at 1.5T. The authors of these studies supposed that carrageenan and sodium azide did not influence the relaxation times of the compositions.

		T1	T2	σ
A	↗	± 0	↘	/
G	↗	↘	± 0	/
N	↗	↗	↘ when G is low ↗ when G is high	↗

Table 4.3: Influence of an increase of agarose (A), gadolinium (G) and sodium chloride (N) on the T1, T2 and conductivity of the CAGN phantom [77] [78]

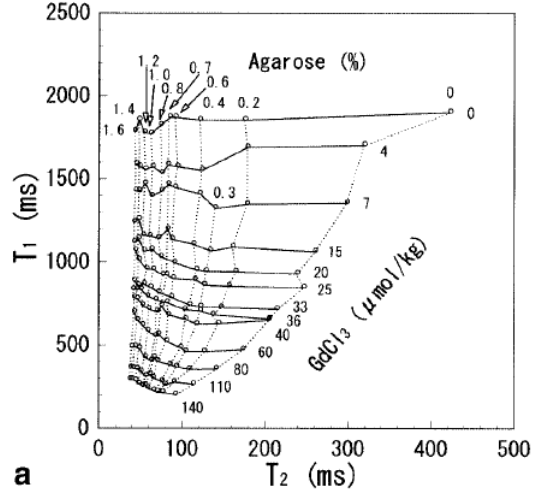


Figure 4.14: T1 and T2 relaxation with respect to G and A. dotted lines correspond to iso-agarose concentrations and solid lines correspond to iso-gadolinium concentrations. [54]

Gel compositions

The compositions of the gels, specific to each tissue surrogate, were derived from the experimental data and models discussed in Hattori et al's publication [58]. The coefficients of the model are specific to the magnetic field strength $\mathbf{B}_0$. Each concentration - agarose (A), gadolinium (G) and sodium chloride (N) - are derived from the relaxation rates ($1/T_1$ and $1/T_2$), which have been evaluated in a previous publication (Table 4.1) based on the Equations 4.2 to 4.7.

$$\frac{1}{T_1} = g(A, G)N + u(A, G) \quad (4.2)$$

$$u(A, G) = a_1 + a_2A + (a_3 + a_4A)G + (a_5 + a_6A + a_7A^2)G^2 \quad (4.3)$$

$$g(A, G) = \frac{e_0 + e_1G + e_2G^2}{1 + \exp(-(A - e_3)/e_4)} + e_5 + e_6G + e_7G^2 \quad (4.4)$$

$$\frac{1}{T_2} = h(A, G)N + v(A, G) \quad (4.5)$$

$$v(A, G) = b_1 + b_2G + b_3G^2 + (b_4 + b_5G)A \quad (4.6)$$

$$h(A, G) = \frac{q_0 + q_1G + q_2G^2}{1 + \exp(-(A - q_3)/q_4)} + q_5 + q_6G + q_7G^2 \quad (4.7)$$

The parameters a_i , b_i , e_i and q_i are dependent on the magnetic field strength and are available in the publications of Kato et al. [48], for 1.5T, and of Hattori et al. [58], for 3.0T. The concentration N (Equation 4.8) is derived according to the Cole-Cole equations.

$$N = \frac{\sigma - c_0 - c_2 \log f - c_4 (\log f)^2}{c_1 + c_3 \log f + c_5 (\log f)^2} \quad (4.8)$$

where σ is the conductivity at the frequency f . The coefficients c_i are independent from the frequency, thus from the magnetic field $\mathbf{B}_0$.

Organ	Gel Composition				
	GdCl3 $\mu\text{mol}/\text{kg}$	Agarose %	Carr. %	NaCl %	NaN3 %
Liver	82.9	1.315	1.2	0.148	0.03
HCC	44	0.638	3	0	0.03
Stomach	34.7	0.895	1	0.371	0.03
Pancreas	97.6	1.22	1	0.291	0.03

Table 4.4: Gel compositions of the four tissue-surrogates to produce

Gel preparation

The gel preparation requires a set of laboratory material, as described in the publication of Seiichiro et al. [55]. First, the components have to be weighted precisely to respect the required concentrations derived from the equations above. Then, the components are soaked in water for at least 12 hours to facilitate dissolution during the next phase of the preparation. The pre-soaked solutions are then heated in turn to dissolve into water and they are mixed to ensure the homogeneity of the solution. Finally, the heated gels have to be gently poured into molds of the shapes of the organs, as described in the next section. Cooling of the gels until the gelling point can be done by simply leaving the solutions at room temperature for a couple of hours. A tumor cooled beforehand was inserted just after pouring the liver-like preparation in the liver molds.

Quantities of powder in grams were determined by a sub-milligram scale⁷ for all the components except gadolinium. The latter one was hydrated and had to be taken with a micropipette. The prepared solutions were stored in pyrex beakers, which could be directly plunged in the heating bath. This heating bath was a fryer⁸ containing cooking oil reaching temperatures of 140°C. A rotating motor⁹ set at 120 rotations per minutes induced the mixing of the preparation by rotating a helix as the ones depicted on Figure 4.15. A mercury thermometer continuously evaluated the temperature of the oil bath. The preparation setting is presented on Figure 4.15

Though the manipulations of the preparation are simple, safety is an imperative requirement at all time. The gel preparation took place under an extraction fan behind a security glass. The manipulations have to be cautiously performed to avoid making mistakes in the required concentrations and to avoid other inconvenience such as the presence of bubbles in the gel or inhomogeneity of the solution.

⁷Sartorius Research, R 200 D; R 180 D-*F1

⁸DO461FR, Domo, Linea 2000, Belgium

⁹Euro ST P CV P7, Ika Werke, Germany

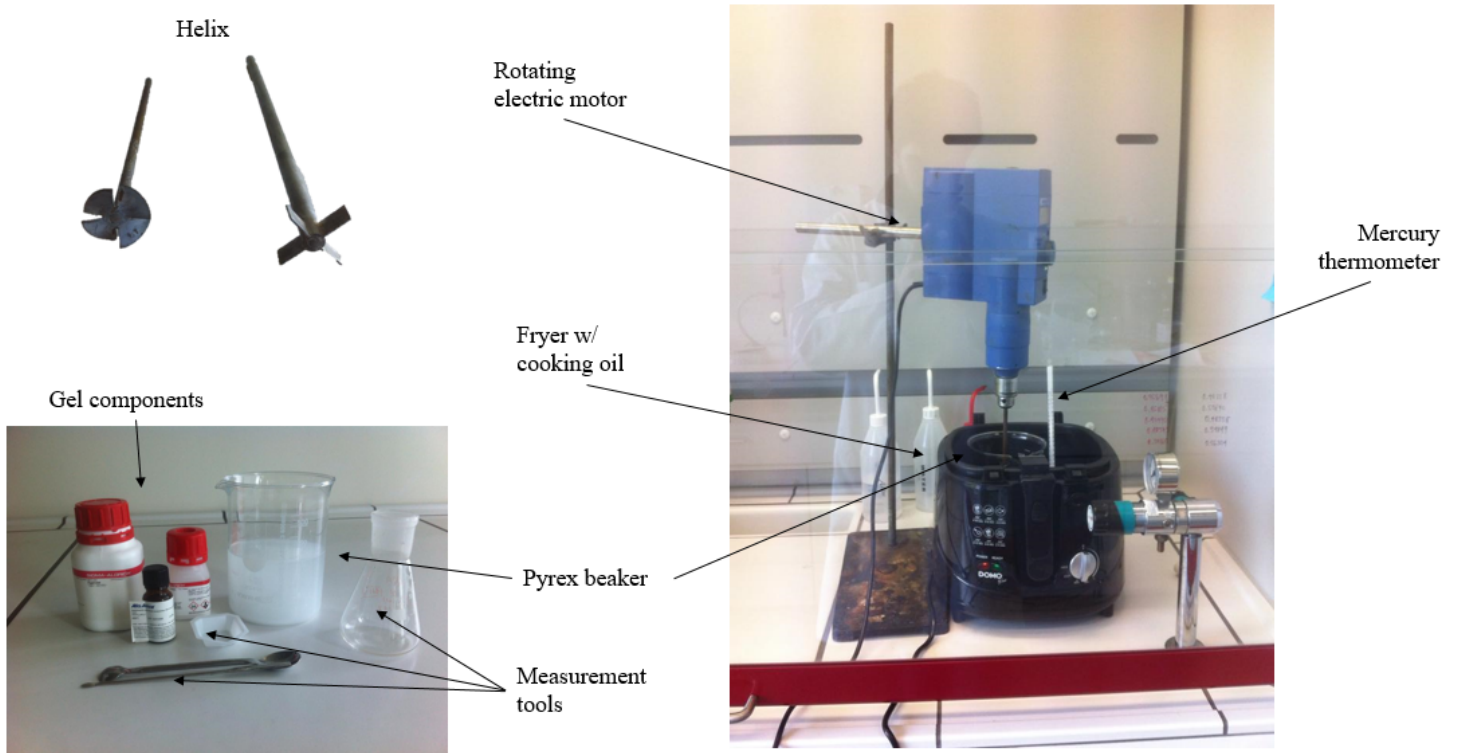


Figure 4.15: Preparation of the gels

5 Molds of the organs

In order to give the gels the shape of the three selected organs and a tumor, molds were made. The first idea was to 3D print numerical meshes derived from medical images with 3D Slicer¹⁰ in rigid plastic to mold them later in plaster and to drip the gels inside. Yet, this would have been more expensive and time-consuming. In addition to these issues, the parts were too big to be printed at once. Taken these problems into account, another solution was chosen. A rigid 3D model as in Figure 4.16 was used as a reference. These organs have the advantage of fitting perfectly with each other (similar to what happens inside a human torso). However, they are smaller than those of an average adult (80% of actual size).

After testing the casting technique, plaster was replaced with silicone because it is much easier to handle, less crumbly and it better adopts the shape of the models. The duplication addition silicone used is the SELACOPY 20 Blue produced by Selection (Figure 4.17). For this product, the use of a vacuum pump to remove bubbles before the pouring is highly recommended.

¹⁰3D Slicer is an image computing platform for quantitative network imaging [79]

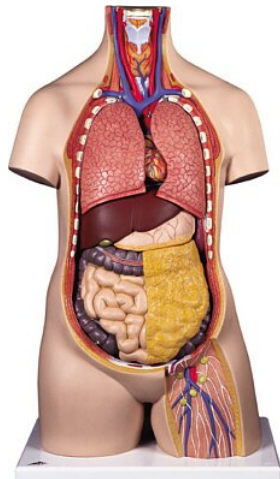


Figure 4.16: Plastic models of a human torso and the abdominal organs



Figure 4.17: Silicone used for the mold of the organs

The molds were made in two parts with a hole in the second part to be able to remove the gel. On Figure 4.18, the mold for the stomach and for the liver can be seen respectively on the left and on the right side of the image. For the tumors, 40mm diameter plastic balls were used and mold following the same steps.



Figure 4.18: On the left : the 2 parts of the mold of the stomach. On the right : the 2 parts of the mold of the liver.

6 Connecting the organs together and to the membrane

To connect the organs together and with the membrane, the first option selected in the design step of the creation was the use of glue and Velcro™ (see Chapt. 3, Sect. 4.4). This solution would have been a close reproduction of the human body. Indeed, the organs are bound one to another (and to the diaphragm) with ligaments which are a collection of small threads overlapping each other in an intricate configuration in the manner of Velcro™. However, it turned out that it was impossible to stick something to the organ-like gels. The second option found was then to use a mold as showed in the Figure 4.19. The organs are placed in this mold which maintains them in the same configuration as they have in the human abdomen (see Figure 4.20). To prevent the organs from shifting out of their place, a rubber band holds the mold and the organs together .

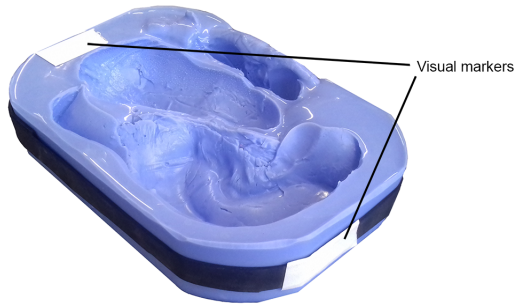


Figure 4.19: Picture of the mold containing the organs

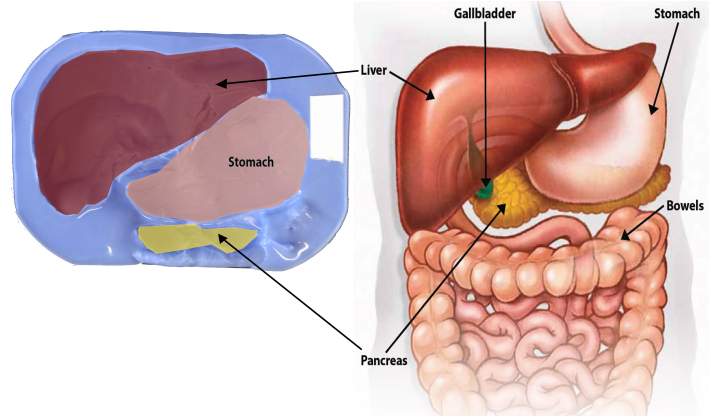


Figure 4.20: The coronal layout of the organs in the mold compared to a upper abdominal representation

Once the organs have the good spatial configuration, they have to be fastened to the membrane. Again, the matter of the mold can be neither glued nor even screwed. The chosen option was to use an elastic strip surrounding the mold (in black on the Figure 4.19) and two plastic hooks glued to the membrane (see Figure 4.21).



Figure 4.21: Picture of the disposition of the plastic hooks stuck to the membrane

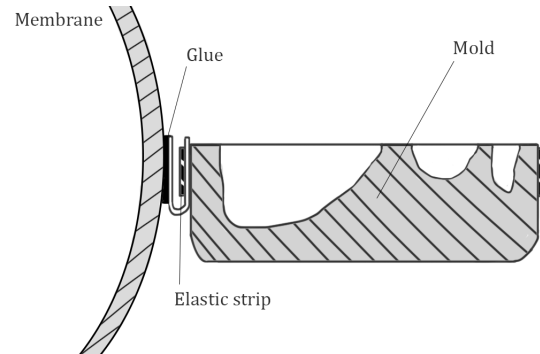


Figure 4.22: Diagram of the fixation system of the mold on the membrane

The Figure 4.22 sketches the way the mold and the elastic strip interlock to unify the membrane and the organs in order to transmit the motion from the first to the second.

7 Visual tracking

Regarding the visual tracking, the original idea was to purchase a MRI-compatible camera tracking the tumor simultaneously with the MR acquisition. However, the price of these cameras exceeds the budget of our master thesis. Therefore, as a first step, we implemented a non-MRI visual tracking. The interest of this tracking was twofold. On the one hand, this prototype served as a proof-of-concept to validate the visual tracking as a reliable method for MR sequence validation. On the other hand, the aim of this tracking was to guarantee the repeatability and reproducibility of the periodic movement throughout several different MR exams. Later, as the tests revealed that the phantom needed an intra-MRI tracking, we borrowed the MRC-system eye-tracking camera [80] of the Saint-Luc university hospital to obtain a real-time image acquisition.

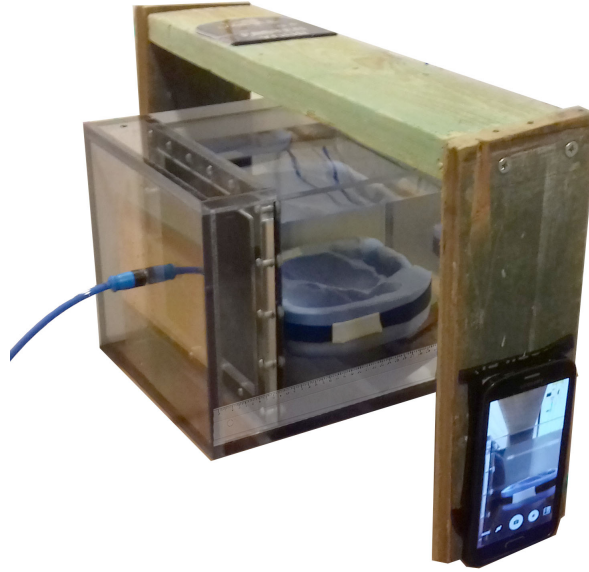


Figure 4.23: Experimental setup for video capture with wooden frame and smartphone

For the recordings outside of the MR chamber, as there was no constraints on the choice of the equipment, a simple smart phone camera was used. The latter was carefully positioned on a wooden frame at two specific positions : On the side of the frame (as it can be seen on the set up in Figure 4.23) for the recording of a sagittal view of the phantom and on top of the frame for the coronal view. Once the videos are recorded, the tracking is done by post-processing the frames using a software developed by Damien Dasnoy-Sumell. With this software we were able to follow the movement at an interface of 2 contrasts. The two pieces of white tape used as visual markers to enhance the contrast with the environment can be seen on Figure 4.19. A graduated ruler placed within the framework of each video and elementary trigonometry was used to compute the amplitude of the movements inside the box. Tracking is only performed on the mold because the location of the tumor relative to the mold can be precisely known by doing a static MRI shot at the the start of the simulation. Moreover we consider this position to be sufficiently constrained such that it will remain unchanged throughout the complete simulation.

The deformations induced by water have not been taken into account as the camera is placed perpendicularly to the interface which is considered to be a flat surface.

For the recording inside the MRI, the camera was placed facing the side of the box. The post-processing of the acquired images is done the same way as explained before. The video recording is launched at the same time as the MR technologist starts the magnetic resonance image acquisition. In the middle, a pause in the movement is made as a time marker.

Chapter 5

Results and discussion¹

After the construction and the tuning of the prototype, the next step was to carry out some tests and experiments on it. These tests were mainly conducted in the MRI machine devoted to UCL research at the Saint-Luc hospital in Brussels (3.0T Achieva: Koninklijke Philips N.V., Best, The Netherlands). The results are divided in two categories :

- Those concerning **the motion of the organs**, to compare with what happens in a real human body and to characterize the repeatability and reproducibility of the movements.
- Those concerning **the material properties of the organs**, specifically, the relaxation times T1 and T2, and the identification of the factors influencing them.

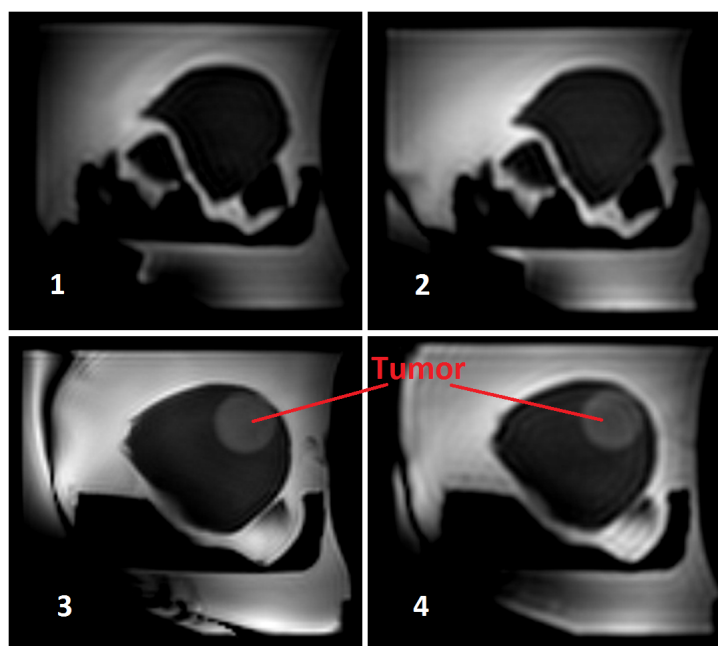


Figure 5.1: Capture of four frames of the MRI videos with different MRI sequence

Four frames of sBFFE sequence (see Chapter 2, Section 4.1) of the sagittal plane of our phantom, with different frequency offsets or acquisition times, can be observed in the Figure 5.1.

¹All the axis (X,Y,Z) used in this chapter refer to the frame introduced in the Figure 4.4. In anatomy, X correspond to the cranio-caudal axis, Y to the sinistro-dexter axis the and Z to the dorso-ventral axis.

These images are taken from image sequences ² which can be observed on this hyperlink ³. On these shots, the membrane is always on the right side of the frame. The position along the Y axis of the first two images is not the same as the last two images. In images 3 and 4, the false tumor is visible inside the liver. Another point worth noticing is the influence of the acquisition parameters on the artifacts and noise.

The comparison between the displacements obtained from the MRI acquisitions and the ones extracted from the camera inside the MRI is displayed Figure 5.2. There is no synchronization between the camera and the MRI acquisitions so the data from the video are fitted on the data from the MRI with the least square method. However, this shows that there is still a good correlation between the two curves, the shape being similar. Nevertheless, a delay is observed between the two curves at some points. These temporal errors are mainly induced by some incompatibilities between the frame encoding of the eye-tracking camera and the recording software that recreates the videos.

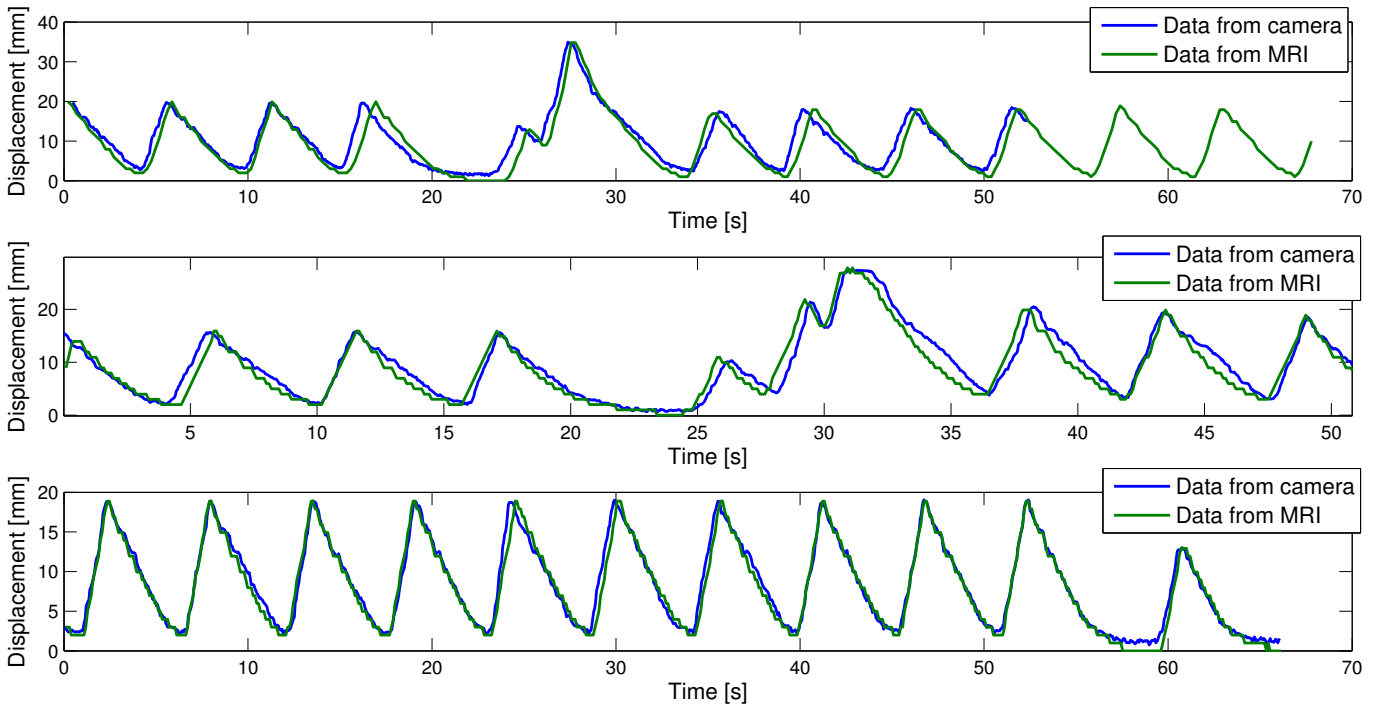


Figure 5.2: Comparison between the motion in the X direction obtained from the MRI and from the eye-tracking camera inside the MRI for three sequences of acquisition

1 Motion test

In order to study the motion of the tumor in the phantom, a series of tests outside the MRI were conducted and recorded with a smartphone camera. A frame of wood was placed against the box to position the smartphone precisely and a ruler fixed on the box allowed to compute the

² The videos corresponding to the frames 1, 2, 3 and 4 are named "*sBFFE_RLT offset0Hz 1200dyn.avi*", "*sBFFE_RLT offset50Hz 600dyn.avi*", "*sBFFE_RLT offset-50Hz 300dyn.avi*" and "*sBFFE_RLT offset-50Hz 600dyn.avi*" respectively

³ <https://drive.google.com/drive/folders/0B2Yu-v7YIDpaMVJvU3ZJek50TkE?usp=sharing>

pixel spacing⁴. The experimental setup is shown in Figure 4.23 and captures of the videos can be seen in the Figure 5.3. The full videos can be seen in the on the web ⁵.

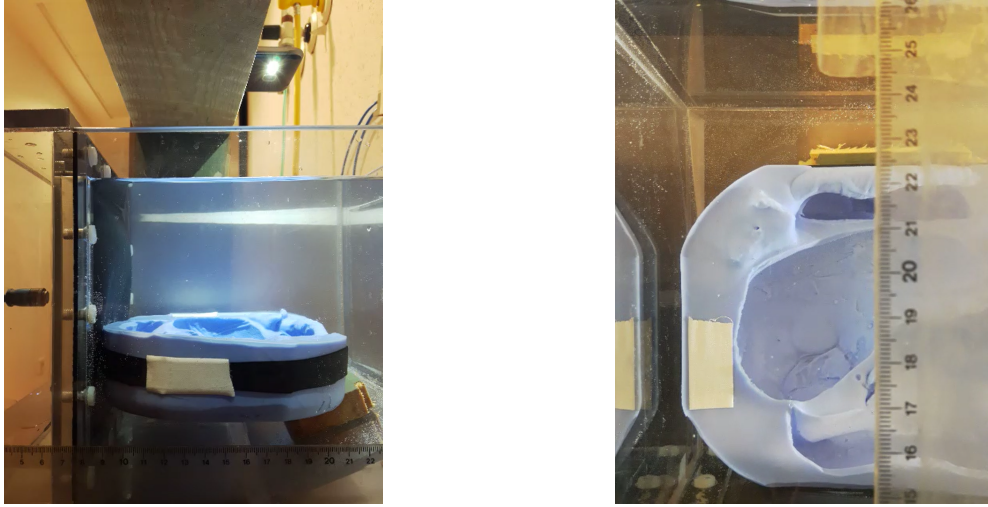


Figure 5.3: Captures of videos of test sequences taken from the side of the box (on the left) and from the top (on the right)

These tests were carried out with the conditions of the hospital ($p_{air\ supply} = 5bar$, $p_{vacuum} = -0.8bar$) but outside the machine. Six sets of tests were recorded from the two recording positions (corresponding to the sagittal and coronal views of an MRI). After each pair of tests, the whole set up was entirely disassembled and reassembled, as described in the Table 5.1.

Set	View	Number of tests
1	Side	5 x 1'
2	Top	5 x 1'
Disassemble and reassemble		
3	Side	3 x 30"
4	Top	3 x 30"
Disassemble and reassemble		
5	Side	3 x 30"
6	Top	3 x 30"

Table 5.1: Description of the tests performed and recorded for the motion of the phantom

For the analysis of the motion, an interface tracking algorithm was used to extract the curves of the displacement along the different axis. An example of the gross output of this algorithm can be seen on the Figure 5.4. A post-treatment with MatlabTM(The MathWorks, Inc.) allows to split the curve into independent breathing cycles, as the one of the Figure 5.6. The first and last cycles of a test sequence are neglected because they are not always complete. A series of characteristic values are drawn from these breathing cycles such as the amplitude of motion, period and ratio between the inspiration and expiration times.

⁴The pixel spacing, in one direction, is the number of millimeter represented by a pixel on the video, along this direction.

⁵Named "Tracking Serie1 Test4 - Side View" and "Tracking Serie4 Test4 - Top View" at : <https://drive.google.com/drive/folders/0B2Yu-v7YIDpaMVJvU3ZJek50TkE?usp=sharing>

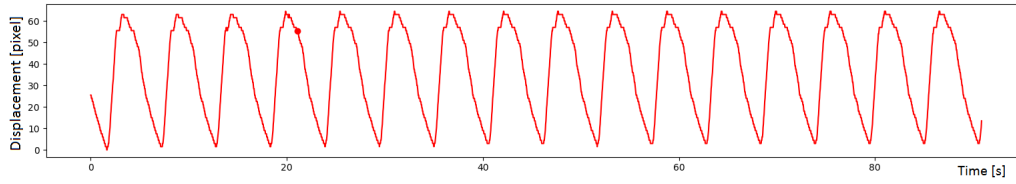


Figure 5.4: Output curves of the visual tracking algorithm used to extract the motion along an axis from the videos

1.1 Similarity with the real human motion

For a good understanding of the results, the parameters on Figure 5.5, representing the evolution of the lung volume during a breathing period, will first be defined. The breathing period, T_{tot} , is divided in two parts: the inspiration time, T_i , and the expiration time, T_e .

T_i is the time elapsed between the first local minimum and maximum of one breathing cycle and T_e is the time between this maximum and the second local minimum.

The maximum amplitude of motion represent the total distance covered in millimeters during T_i .

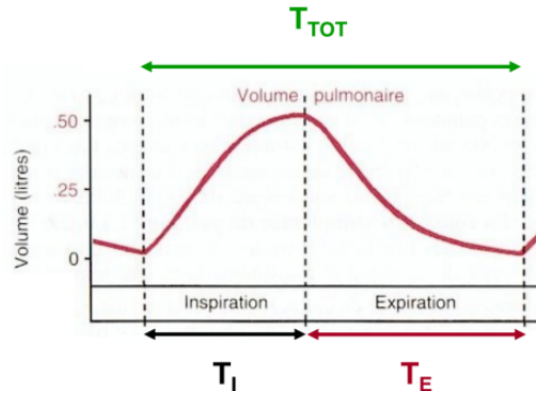


Figure 5.5: Evolution of the human respiratory volume across time[81]

Assuming that the lung volume is directly related to the position of the diaphragm, the amplitude of the membrane in the x-direction of our phantom during a breathing cycle is compared to the variation of the pulmonary filling on a breathing cycle (Figure 5.6 and 5.5). The shapes of the curves are quite similar. The major difference concerns the relationship between inspiration and exhalation. For an adult human at rest, inspiration represents 0.33% of the total cycle time [81]. However, the duty cycle of the electro-valve of our phantom had to be fixed at 0.27% in order to reach a maximum amplitude of movement.

Concerning this amplitude, our phantom generally reaches values slightly below the objective of 20 mm (varying from 12.8 to 20.1 mm as presented in the next section). Furthermore, the respiratory period is set to 5.56 seconds. In comparison, the duration of the respiratory cycle for the adult at rest varies between 4 and 5 seconds. Constrained by the vacuum pressure of the hospital and the maximal flow rate of the electro-valve, our phantom could not return to the initial state in less than four seconds. A compromise has been made to decrease the period as much as possible, without reducing the amplitude too much while remaining with a consistent duty cycle. Nonetheless, these values remain acceptable for the simulation of human respiration.

On this hyperlink ⁶, the video called *Sagittal_Comparaison.avi* compares a sagittal MRI-acquisition of a human patient and sagittal MRI-acquisition of our phantom.

⁶<https://drive.google.com/drive/folders/0B2Yu-v7YIDpaMVJvU3ZJek50TkE?usp=sharing>

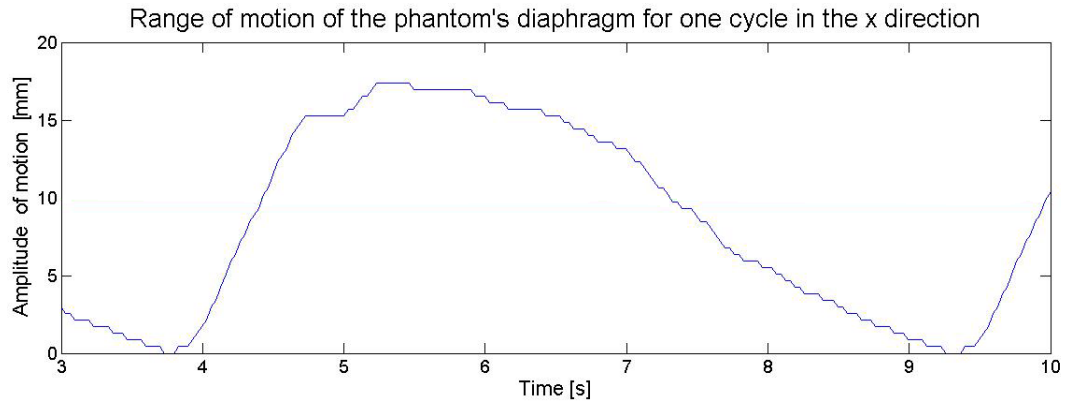


Figure 5.6: Evolution of the amplitude of motion in the x direction for one respiration cycle across time

1.2 Repeatability and reproducibility of the motion

The reproducibility of the breathing motion can be analyzed by the comparison between the sets 1-3-5 and sets 2-4-6 because they are recorded from the same angle respectively with a dismantling and a reassembling of the setup between each (see Table 5.1). On the other hand, the repeatability can be characterized by the comparison of the cycles of respiration within each set.

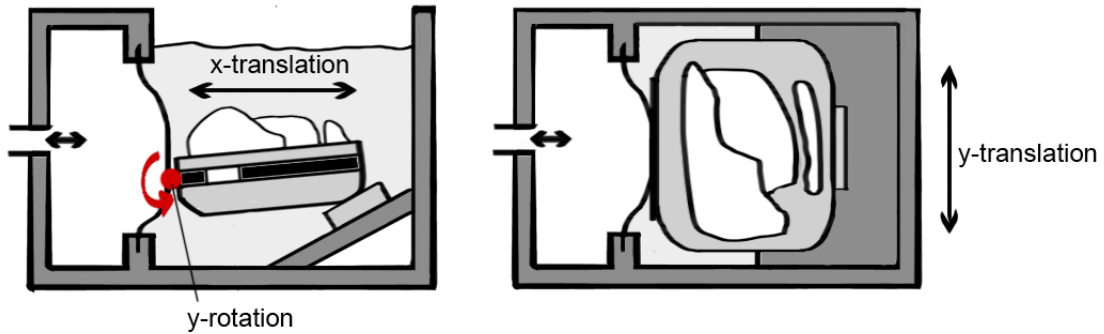


Figure 5.7: Decomposition of the motion in three directions : two translations along X and Y and one rotation around Y

Thanks to the recordings from two different positions, it is possible to analyze the motion in 3D. It will be done by decomposing the motion (see Figure 5.7) in two translations along the axis (X,Y) and one rotation around the Y axis of the frame introduced in the Figure 4.4. The center of the Y-rotation are the ties linking the molds to the membrane (The red dot on Figure 5.7). Thus, the displacement of the organs along the X axis and around the Y axis can be tracked from the sets of videos 1, 3 and 5, while the sets 2, 4 and 6 are used for the translation along the X and Y directions.

1.2.1 Translation in the X direction⁷

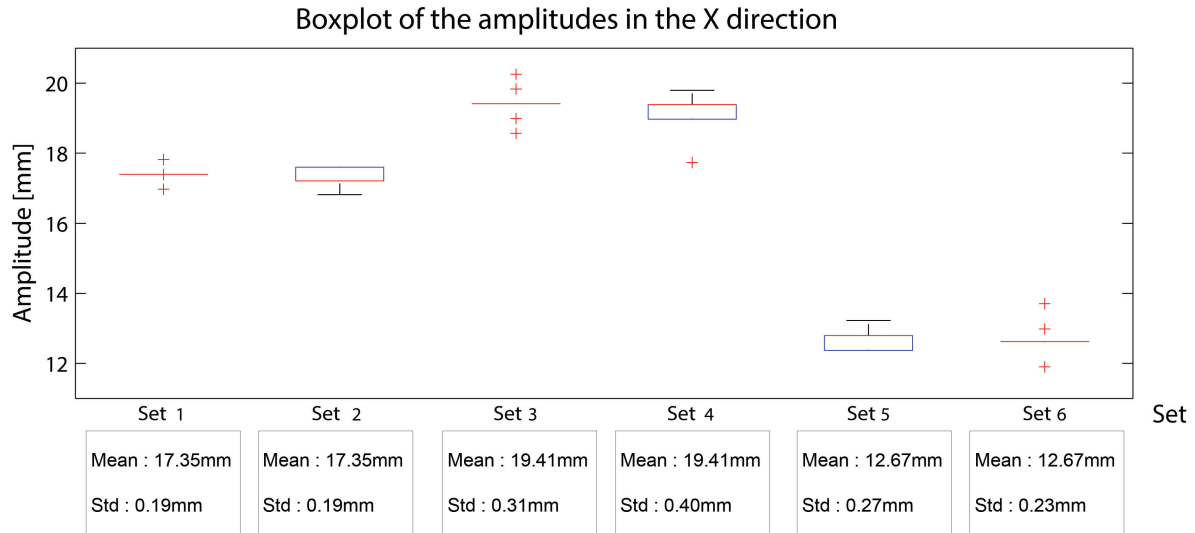


Figure 5.8: Boxplot of the amplitude of the motion for each set

Figure 5.8 shows the boxplot of the amplitude of the motion in the X direction. Different observations can be done from this figure.

First, all the standard deviation of each set (mentioned in the frame below the diagram) are lower than 0.4mm, which is smaller than the limit value of 1mm stated in the requirements (Chapter 3, Section 2). This proves that the repeatability of motion over time guarantees enough precision once the setup is assembled and working.

Secondly, the average amplitudes of the motion are different between the sets when the setup is disassembled and reassembled. For example, between the set 3 and 5, the difference reaches 6.74mm, which is far over the required precision.

For the comparison of the set when the setup remains assembled, the size of the box (gap between the percentile 25 and 75) of the sets 2 and 4 are bigger than the ones of the sets 1 and 3. This can be explained by the circumstances of the top position recording. Indeed, the waves induced by the motion at the surface of the water create some distortions in the image, introducing noise that spread the distribution of the amplitudes.

Concerning the fifth set, the noise can be explained by the recording environment as someone walked next to the device which slightly shook the camera.

The last set is very neat despite the waves in the water. Indeed, since the amplitude of the motion is smaller, the waves are smaller too and disturb less the quality of the images.

The conclusion that can be drawn from this analysis is that, whenever the setup is disassembled, a camera is needed to calibrate the motion detection. Nonetheless, concerning the amplitude, if the device is not disassembled nor modified, it seems that we can consider that the motion remains identical as the first 30 seconds.

⁷For the sake of clarity and in order to simplify the analysis, the boxplot or curves represented on Figures 5.8, 5.9, 5.10, 5.11, 5.12 and 5.13 are derived for the data of all the tests inside one set respectively.

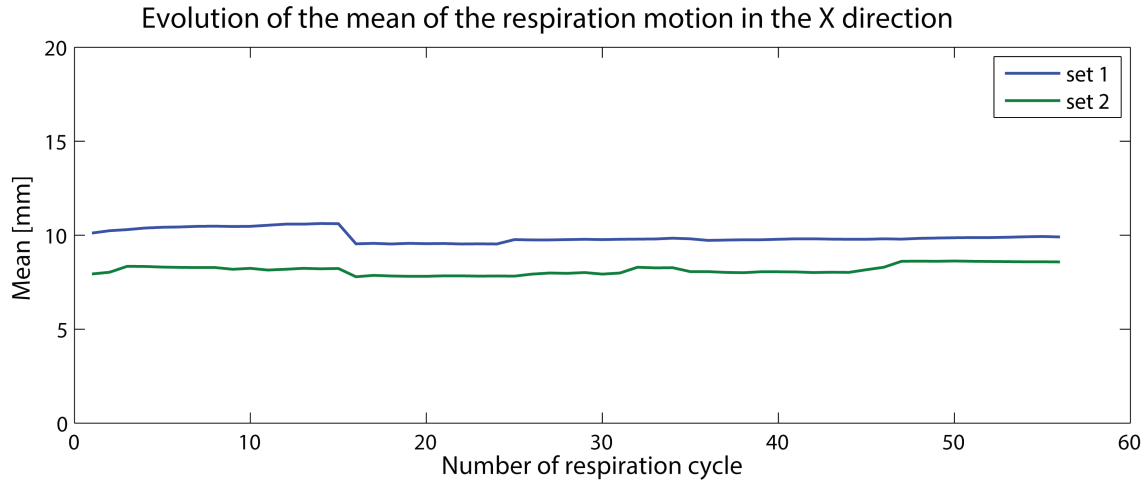


Figure 5.9: Evolution of the mean of the respiration cycles over time

To assess the stability of the motion over a long period, the first two sets were examined. We were afraid the motion would be variable over time because of the slow inflation or deflation of the membrane. To analyze this, the mean amplitude of motion for each cycle of respiration is plotted in the Figure 5.9. Each respiration cycle lasts about 5.56 seconds. The total time of the tests, accounting the pauses between each of them, covered about 10 minutes.

The curves on Fig. 5.9 show us that there is no real evolution of the means and the long term motion can be considered as stable.

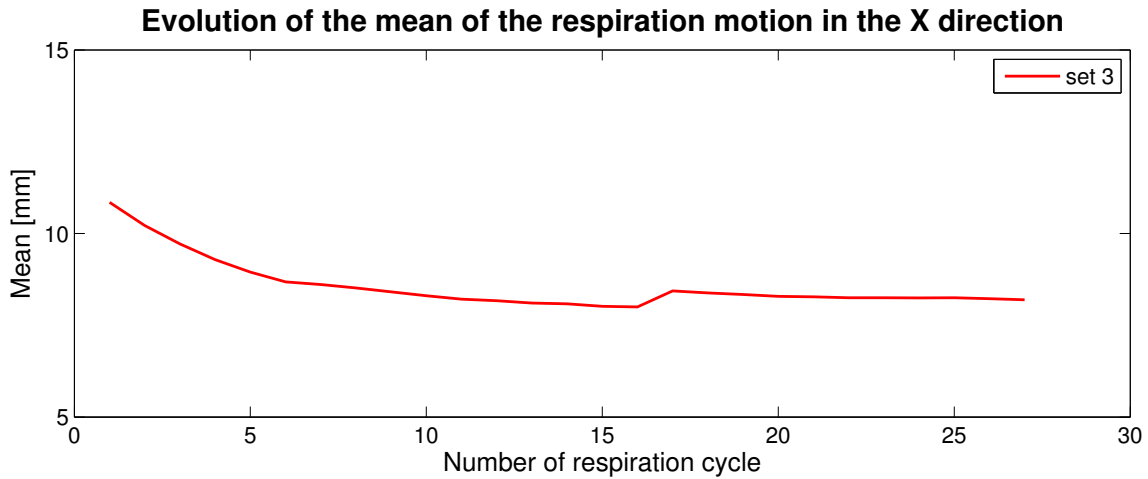


Figure 5.10: Evolution of the average of the displacement induced by the respiration cycles over time after an inflating step

In the Figure 5.10, the membrane was over-inflated at the start of the test. Even so, the mean of the respiration cycles decreases following an exponential shape. This leads us to the conclusion that the system comes back to its stable position after a disturbance (excessive inflating or deflating of the membrane). Other tests were performed and confirmed this conclusion (see Appendix F). The inflating or deflating of the membrane is physically limited due to the shape of the box and by the available pressure range.

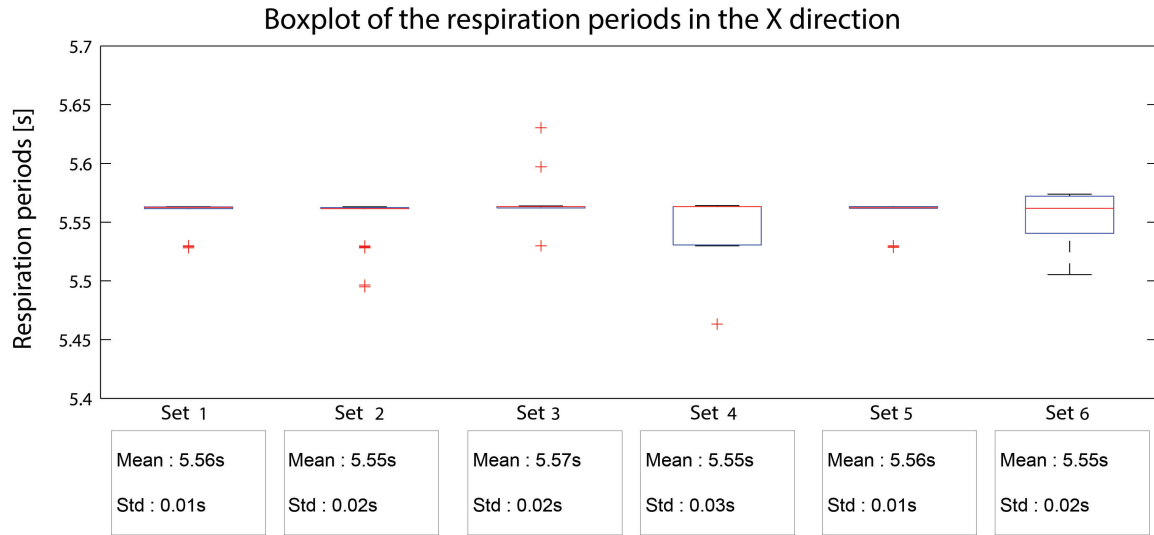


Figure 5.11: Boxplot of the period of respiration cycles for each set

The Figure 5.11 illustrates the boxplots of the periods of the respiration cycles for each set. Given the results, we can say that the period is 5.56 seconds. Again, the sets 4 and 6 have a bigger standard deviation that can be explained by the waves at the surface of the water. But this standard deviation ($<0.035s$) is still acceptable, knowing that the temporal resolution of the MRI is of about 0.1 to 0.2 seconds for the used sequences.

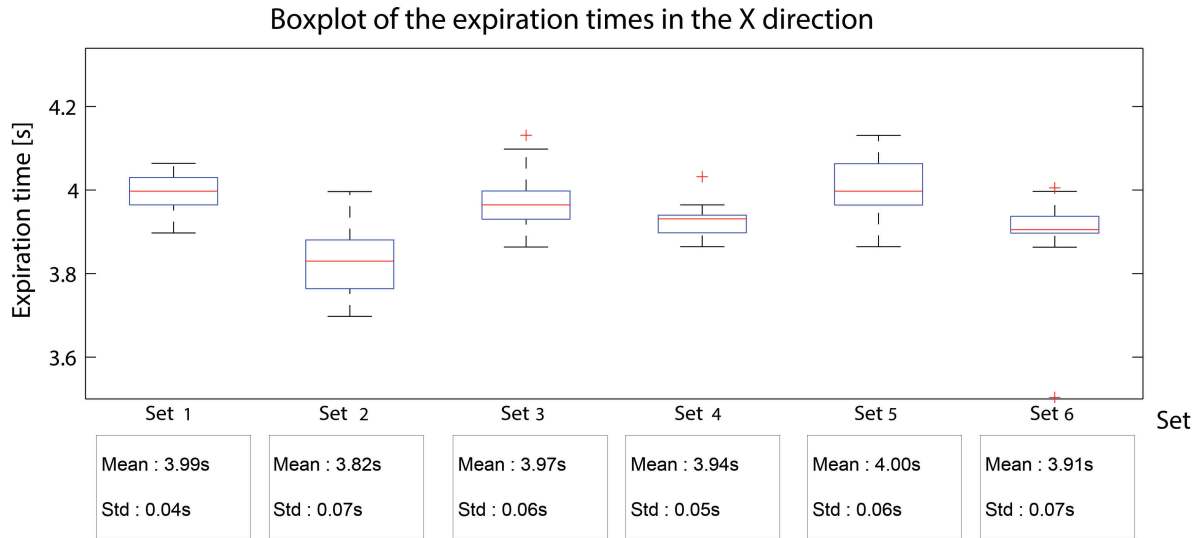


Figure 5.12: Boxplot of the expiration time for each set

The last analyzed variable for the X direction of the motion is the expiration time. The Figure 5.12 shows the boxplots of the distribution of this variable for each set. As the respiration period is the sum of the inspiration and expiration time and that the precision of this period was proved higher, we can conclude that the plotting of the inspiration time would lead us to the same results.

Is it visible that all the expiration times are included between 3.69s and 4.13s, which gives a temporal precision of 0.22s, no matter the query set. Inside the sets, the standard deviations are lower than 0.12s.

Thus, for the inspiration/expiration times and for the periods, there is enough repeatability and reproducibility with respect to the requirements.

1.2.2 Translation in the Y direction

The amplitude of the noise introduced with the water movements is quite the same as the amplitude of the motion in the Y direction. This can be seen on the video and the analyze gives a motion of less than 0.35mm, 1.35mm and 0.77mm in the sets 2, 4 and 6 respectively. Due to these results, the Y direction of the translational motion will be neglected.

1.2.3 Rotation around the Y axis

In this section, the amplitude of the rotation will be detailed. The temporal evolution of the data is directly correlated to the data described in the Section 1.2.1 of this chapter and will not be furtherly commented.

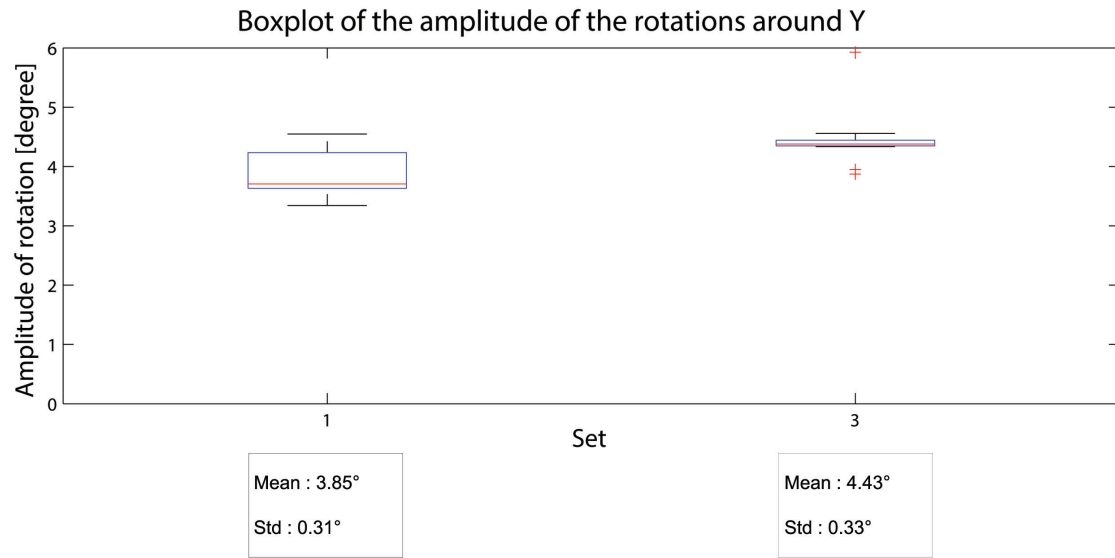


Figure 5.13: Boxplot of the rotation amplitudes for each set

The Figure 5.13 shows the boxplots of the rotation amplitudes around the Y axis for the sets 1 and 3. The data of the set 5 are not represented because of a problem with the extraction of the data with the algorithm of visual tracking that we did not manage to overcome.

Based on the results displayed by the boxplots, we can make some observations that are nearly similar to the ones drawn with the X translation. Indeed, the standard deviation for the two sets are lower than 0.33°. On the side of the mold opposite to the membrane, this rotation is equivalent to a mean amplitude in the Z direction of 9.74mm and 11.19mm for the sets 1 and 3 respectively. The associated standard deviations in millimeters are 0.79mm and 0.84mm, which correspond to the worst cases. Given a required precision of 1mm, this motion is considered repeatable for the application.

However, as it is the case for the X translation, the motion is also not reproducible enough for the Y rotation, the difference of the average amplitude between the sets being of 0.58°, with gives 1.47mm in the Z direction for the end of the mold.

Note The similarities with the X-translation are consistent because the rotation and the translation are linked by the geometry of the box. The ties on the membrane have only a motion in the X-direction and they are the point of rotation of the mold. At the other side, the mold slides along the slope of the box. So, the Y-rotation (angle β on the Figure 5.14) can be extracted from the X-translation and the dimensions of the box.

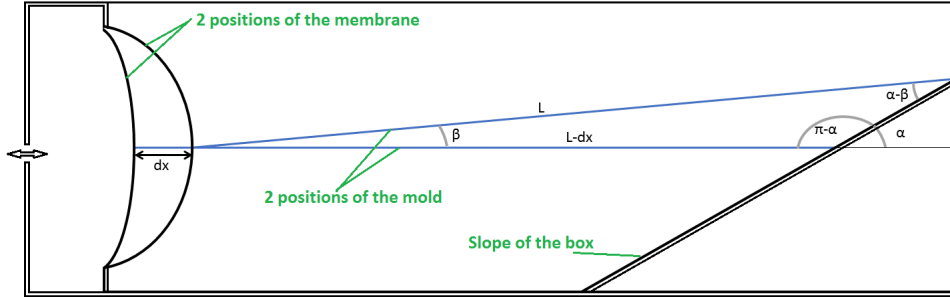


Figure 5.14: Schematic of the box with the membrane deflated and inflated. dx is the X-displacement of the membrane, L is the length of the mold (145mm) and α is the slope of the bottom of the box (21.8°)

With the notations from the Figure 5.14, the rotation as function of the X-translation (dx) is given by:

$$\beta = \alpha - \sin^{-1} \left(\frac{L - dx}{L} * \sin(\alpha) \right) \quad (5.1)$$

The Figure 5.15 shows that the two methods give nearly the same results – less than 0.25° of difference – and are so considered as equivalent.

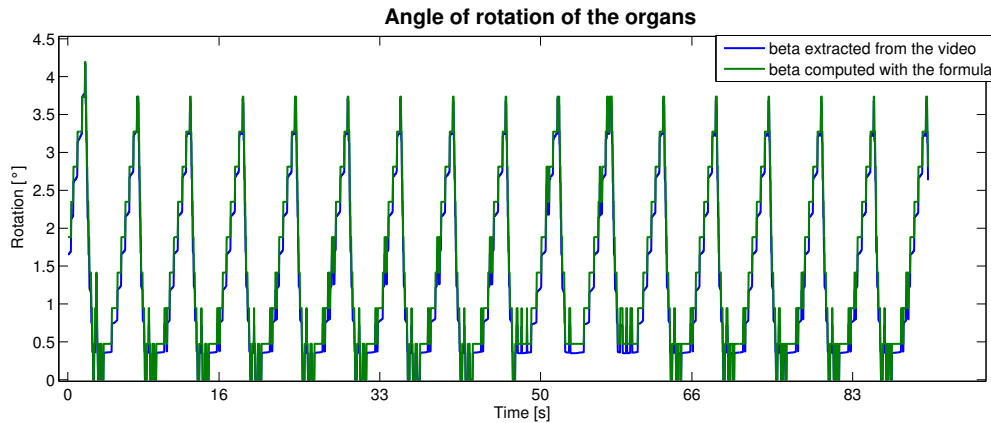


Figure 5.15: Comparison between the rotation angle obtained by the formula and extracted from the video. The data come from the set 1 - test 1.

2 Tissue surrogates

According to the procedure described in the publication of Seiichiro et al. (2008, [55]), a series of gel organs and gel samples were produced with the compositions of the *CAGN phantom* prescribed by Hattori et al. (2013, [58]). As a quick reminder, the objectives aimed by the gels concerned the replication of human tissue relaxation times and dielectric properties, the ability to mimick the organs in shape and to enable the visual tracking of the tumor. These goals go along with expectations on the quality and the budget enlisted in our master thesis. The proper definition of these points is given in Chapter 4 Section 4. They will be commented all along of

this section. However, the dielectric properties of the gels will not be assessed in the context of our master thesis and will only be discussed at the end of this chapter.

First, a set of 14 organ-like gels has been prepared to evaluate the relevance of the use of the *CAGN phantom* for real-time imaging calibration. Then, a batch of 33 samples has been used to assess the influence of carrageenan and sodium chloride on the relaxation times of fixed compositions of agarose and gadolinium. Previous research had considered the effect of sodium chloride to be linear and had neglected the influence of carrageenan on the T1 and T2 values [77][78]. The homogeneity and the precision in the measures have also been evaluated through these samples.



Figure 5.16: Organ-like gels prepared for an MRI scan (left) and test samples (right)

For the purpose of sorting the data, the products realized for the tests described below are named after a nomenclature proper to this research. Organ-like gels are listed in terms of their shape and the tissue they endeavor to mimic. There are no specific rules regarding the designation of the latter. On the other hand, test samples are categorized on the basis of their compositions. In total, 3 preparations of *a priori* the same initial compositions were prepared. They are differentiated in preparation 1, preparation 2 and preparation 3. The letters C, A, G and N determine the components present in the final preparation (C for carrageenan, A for agarose, G for gadolinium and N for sodium chloride). Each sample contains the same concentration of A and G but C and N may vary from one sample to another. Within a final set of samples (AG, CAG, AGN or CAGN), the items are numbered from 1 to the amount of samples of this series (with either one or two varying parameters)⁸.

2.1 Organ-like gels

The organ-like gels (referred as "the organs" in the rest of the section) are sufficiently resistant to be casted in appropriate shapes and to be manipulated by hand. Nevertheless, they remain fragile and must be handled cautiously. They have to be preserved in food-grade plastic film or other laboratory-grade films to avoid drying up (Fig. 5.17) and to avoid any possible ion exchange in the aqueous environment of the phantom.

⁸Example : CAG2.3 is the third sample of a carrageenan-agarose-gadolinium composition from the second batch. The concentration of carrageenan is the only varying parameter in the CAG2 set and is equivalent to 1.5% in this case. All the samples are classified in tables in Appendix G

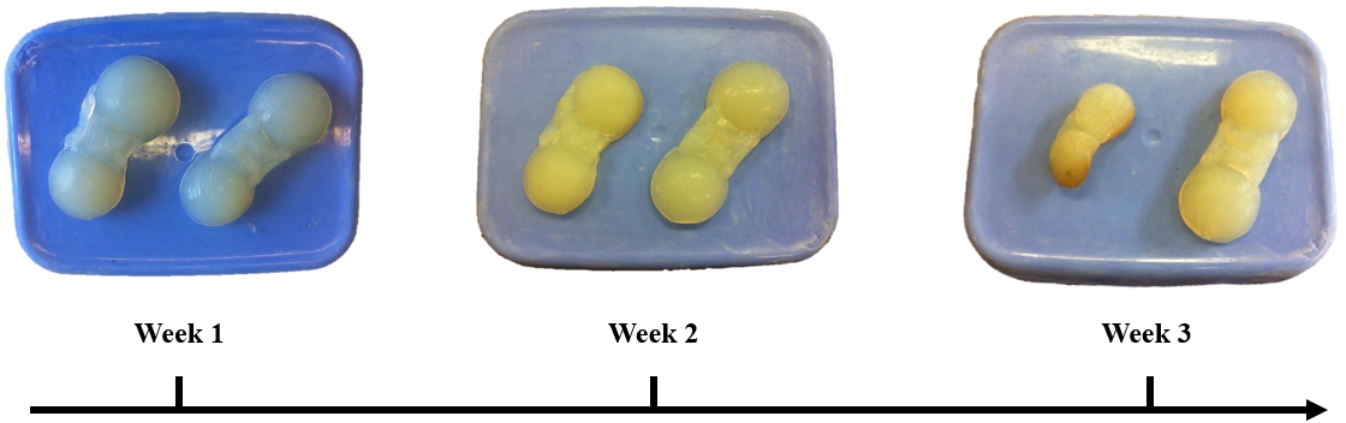


Figure 5.17: Evolution of two gel samples of the same composition over 3 weeks, starting from the week of the preparation. The sample on the left on each image was preserved as it is, the one on the right was preserved in food-grade plastic film between each photo shoot.

Unfortunately, they are not as transparent as expected. However, the tumors that we placed in the livers were visible (Fig. 5.18). The composition of the tumor is much more opaque than the one of the liver because its concentration in carrageenan is higher ($C_T = 3\%$, $C_L = 1.2\%$). Transparency of the gels can be slightly enhanced by decreasing the concentration in carrageenan in the preparation initially prescribed by Kato et al. (2005, [48]), as it has been done in the stomachs ($C = 1\%$), pancreas ($C = 1\%$) and livers ($C = 1.2\%$). Yet, the solidity of these gels is impacted in return. Transparency is also related to the dissolution of the components of the gels in the water during the preparation. The temperature of the solution has to be brought at 100°C to enable the complete dissolution of agarose. Once the T2-modifier has been dissolved, the solution becomes totally clear. The carrageenan may be added at that moment. In order to improve the dissolution of this latter, it is recommended to pre-soak it the day before in a alcohol-based solution.

Effective dissolution of the gelling agents is also essential to ensure the homogeneity of the solution. In our case, it was essentially limited by the operating mode of the fryer, which served as a heating bath, by the gel container in Pyrex glass and by the helix.

Indeed, the fryer is programmed to follow an "on and off" heating cycle to avoid bringing the temperature of the oil to the smoke point [82]. The temperature of the oil fluctuated from 100°C to 140°C , which may have negatively impacted the temperature of the solution inside the beaker. The beaker in Pyrex glass has a thermal conductivity ($k = 1.005\text{W}/(\text{mK})$, [83]) lower than the one of a porcelain container ($k = 1.5\text{W}/(\text{mK})$, [83]), which was used in the experiments of Seiichiro et al. (2008, [55]).

The mixing of the solution could be improved by changing the helix used or by applying orbital mixing between different heating phases [84]. This improvement could also reduce the amount of air bubbles produced during the mixing phase, which degrade the magnetic properties of the gels.

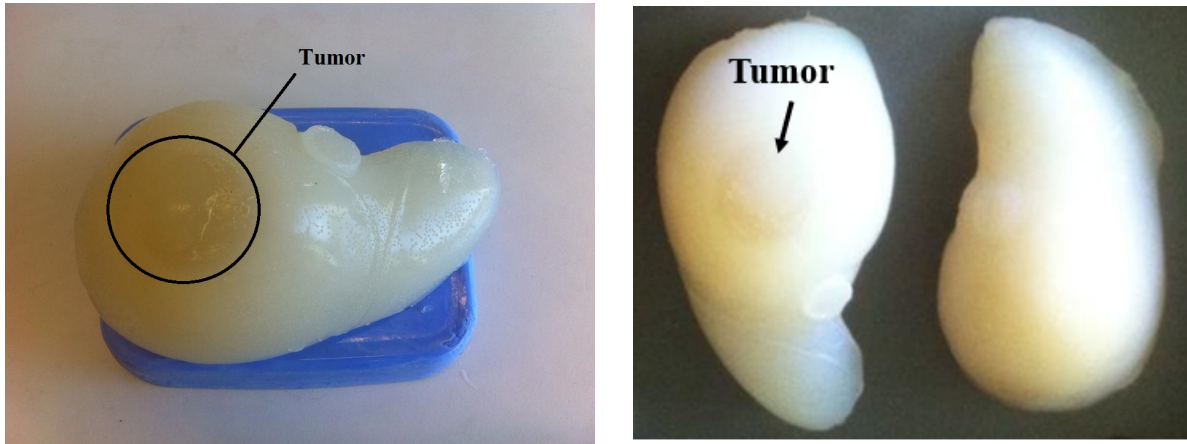


Figure 5.18: Liver-like gel with a tumor inside. The liver surrogate is compared to another liver without tumor.

In addition to having distinctive shapes, the organs are also distinguishable by contrast on MR images at room temperature. This characteristic is essential since it is on the basis of the contrast that the doctors establish their diagnostic. However, the contrasts regarding the gels, depending on the T1 and T2 values (see Chapter 4 Section 4), are not equivalent to the ones relative to human organs as illustrated in Table 5.2.

Tissue	Theoretical		Observed		Gel Composition				
	T1 ms	T2 ms	T1 ms	T2 ms	GdCl3 $\mu\text{mol/kg}$	Agarose %	Carr. %	NaCl %	NaN3 %
Liver	812	42	1252.2 ± 128	67.2 ± 6	82.9	1.315	1.2	0.148	0.03
HCC	1217	74	483.2 ± 107.8	65.25 ± 12.9	44	0.638	3	0	0.03
Stomach	1328	61	1660 ± 319.8	89.1 ± 6.8	34.7	0.895	1	0.371	0.03
Pancreas	725	43	458.7	39.3 ± 2.1	97.6	1.22	1	0.291	0.03

Table 5.2: Comparison between the theoretical and the observed relaxation times (at 3.0T) of the tissue surrogates with respect to their compositions

Additionally to this problem, the gels supposed to represent the same tissue types (liver, stomach⁹, pancreas or tumor) have different mean relaxation times T1 and T2 (Figure 5.19). Large volumes of solution had to be mixed, which has complicated the task of efficiently dispersing all the components in the solution. Moreover, the quantities of components were very small compared to the volume of water in the gel. This may have led to precision errors during the measurements and during the mixing phases (pre-soaking and heating). The problems related to the heating of the solution, as explained above, surely impact the relaxation times of the organ-like gels too, as they influence the homogeneity and the efficiency of the mixture. It is also the case of the air bubbles contained within the gels because they have the relaxation times of air and not of the gels. A solution to minimize this issue could be the use of a vacuum pump to extract the bubbles when the mixture is still liquid. The divergence between the magnetic properties of the

⁹recall that the T1 and T2 values correspond to the spleen due to the lack of data for the stomach

gels compared to the ones of real organs may also be explained by the uncontrolled evaporation of water during the heating phases of the preparation. This issue has been taken in charge in previous works (Seiichiro et al. [55] and Nieburh et al. [46]) by adding water beforehand or by compensating the loss afterwards. In both cases, there is a risk to impair the concentrations.

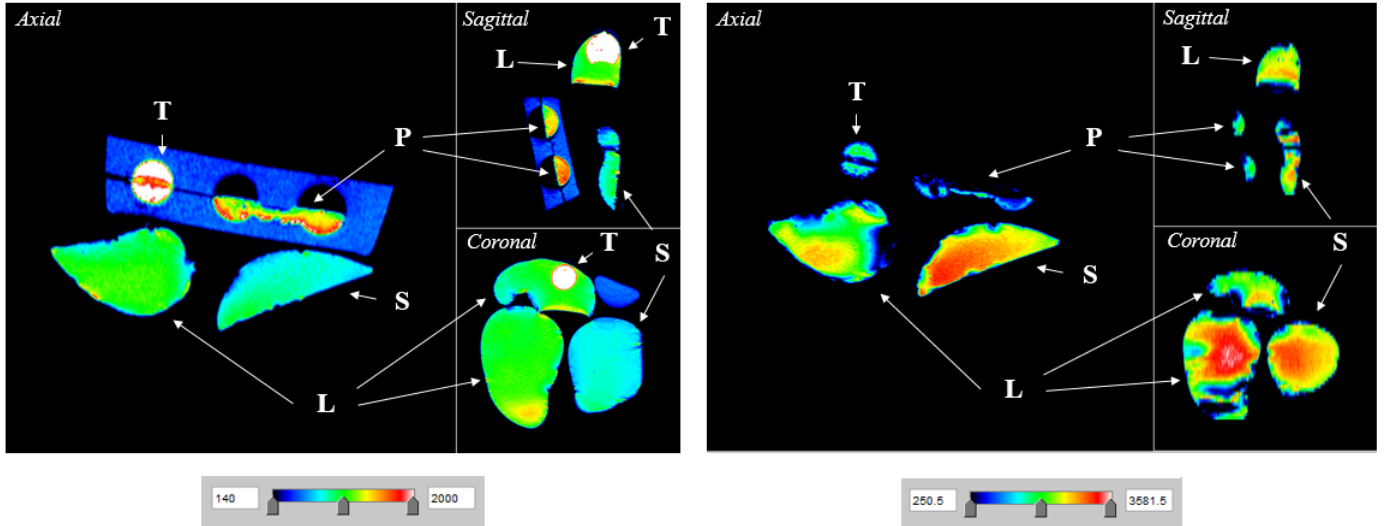


Figure 5.19: Axial, Sagittal and Coronal views of T1-weighted (left) and T2-weighted (right) 3D FFE scans of 2 livers – L – (one with a tumor – T –), 1 stomach – S –, 2 pancreas – P – and an isolated tumor – T –. Images obtained via the Mango software from the Research Imaging Institute, UTHSCSA

The inhomogeneities in the preparations are obvious on the MR images (Figure 5.19) and visible to the naked eye. Figure 5.20 displays the evolution of rot within a liver-like gel. Two of the 14 organ-like gels presented this issue. This must have happened because the sodium azide (NaN_3 - an antiseptic) has not been perfectly dispersed throughout the entire batch of liver preparation.



Figure 5.20: Evolution of the rot on a liver-like gel

A final reason for the differences between the observed and the theoretical values concerning the relaxation times T_1 and T_2 may be related to the experimental character of the model used to predict these values. The conditions in which the gels had been prepared in other studies are apparently not exactly reproduced in our case. A better understanding of the mechanisms of the interactions between the different components of the gels and their influence on their magnetic

properties should help us to improve our results in further research.

Therefore, in addition to the problems met because of the lack of homogeneity and precision with the preparations, variations in the relaxation times may be caused by the presence of sodium chloride and carrageenan in the compounds. These two components were added to simulate the dielectric properties of human organs and to strengthen the gels respectively, which is necessary in the case of studying MRI-GPT. Though their influence has been supposed to be controlled concerning sodium chloride and negligible concerning carrageenan, we evaluated their effect on relaxation times in our case.

2.2 Test samples

A series of tests were conducted to evaluate the influence of carrageenan and sodium chloride (NaCl) on the T1 and T2 relaxation times of agarose-gadolinium- NaN_3 preparations. Three initial preparations of 210 mL (1), 90mL (2) and 100mL (3) of $97.6\mu\text{mol/kg}$ of GdCl_3 , 1.22% of agarose and 0.03% of NaN_3 were divided into 33 samples (8, 5 and 20 samples of preparation 1, 2 and 3 respectively) with varying concentrations of carrageenan and sodium chloride. The statistic tests produced on the data are ANOVA tests (one factor) achieved by Microsoft ExcelTM(2016). The medical images are displayed with the Mango software from the Research Imaging Institute, UTHSCSA, and the boxplots are computed in MatlabTM (The MathWorks, Inc.).

To assess the equivalence of the preparations, each initial compound (1, 2 and 3; $C = 0$, $N = 0$) has been compared to the others. It comes out that within the same set (ex: 3 samples of 1), the preparation seems equivalent. However, the three preparations are different from each other, as it appears clearly on Figure 5.21. The lack of homogeneity throughout sample AG2 appears on the histogram as the values spread very far from the mean value of the sample.

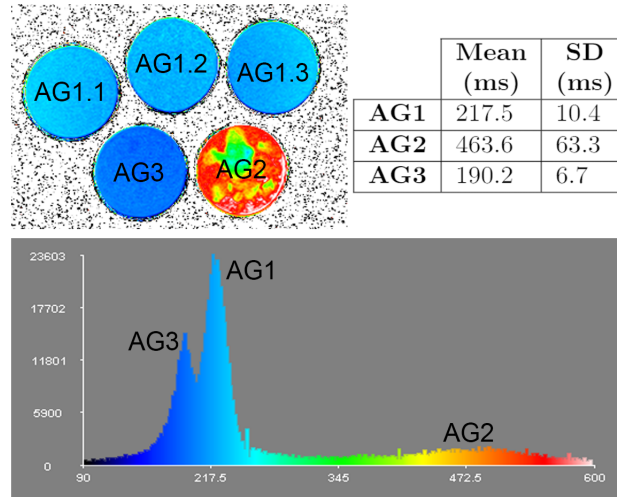


Figure 5.21: T1 mapping of test samples of different initial compositions

Repeated tests of the T1 and T2 values of AG1.2 and AG3.1 gave us an idea of the error margin within a set of measures (Table 5.3). The average T1 values of AG1.2 and AG3.1 recorded across several mappings are surprisingly greater than ones recorded on the single image sequence on Figure 5.21 ($\Delta_{AG1}^{T1} = 47.6\text{ms}$, $\Delta_{AG3}^{T1} = 15.81\text{ms}$). The difference between the averages seems significant in the case of AG1.2 ($p_{\text{value}} = 3.4 \times 10^{-6}$, $\alpha = 0.05$) but we are not confident enough to say the same about AG3.1 ($p_{\text{value}} = 0.07$, $\alpha = 0.05$). However, the increase of T1 along repeated mappings is not steady, the pattern seems to be rather random. Concerning the T2 values, the mean value computed over repeated mapping of the same sample seems to be unchanged ($\Delta_{AG1}^{T2} = 73.7 - 70.6 = 3.1\text{ms}$, $\Delta_{AG3}^{T2} = 68 - 67.1 = 0.9\text{ms}$). Both p-values are greater than 0.5,

which is much greater than the level of significance fixed at $\alpha = 0.05$. A small fraction of the changes in T1 may be related to the heating of the samples through the measures [85]. The majority of these divergences can be explained by human errors during the process (samples not exactly aligned with each other, ROI accounts the container's relaxation times, samples not exactly placed at the center of the magnetic field, ...).

	T1 (ms)	T2 (ms)
AG1.2	$265,1 \pm 29.2$	70.6 ± 4.3
AG3.1	206.01 ± 25.9	67.1 ± 3.7

Table 5.3: Mean values of T1-T2 across 7 images (AG1.2) and 6 images (AG3.1)

The influence of NaCl alone on the relaxation times was studied on the composition AG1¹⁰. It appears clearly on Figure 5.22, that there is a significant difference between the T1 relaxations of a composition with NaCl (AGN) and without NaCl (AG). However, the variations related to the increasing concentrations of NaCl throughout the samples do not follow a linear tendency as predicted by Hattori et al. (2008, [58]). The same analysis is done regarding the T2 values, except that there is no significant difference between samples with and without NaCl. NaCl seems to have less influence on T2 than on T1, as expressed by Hattori et al. (2008, [58]).

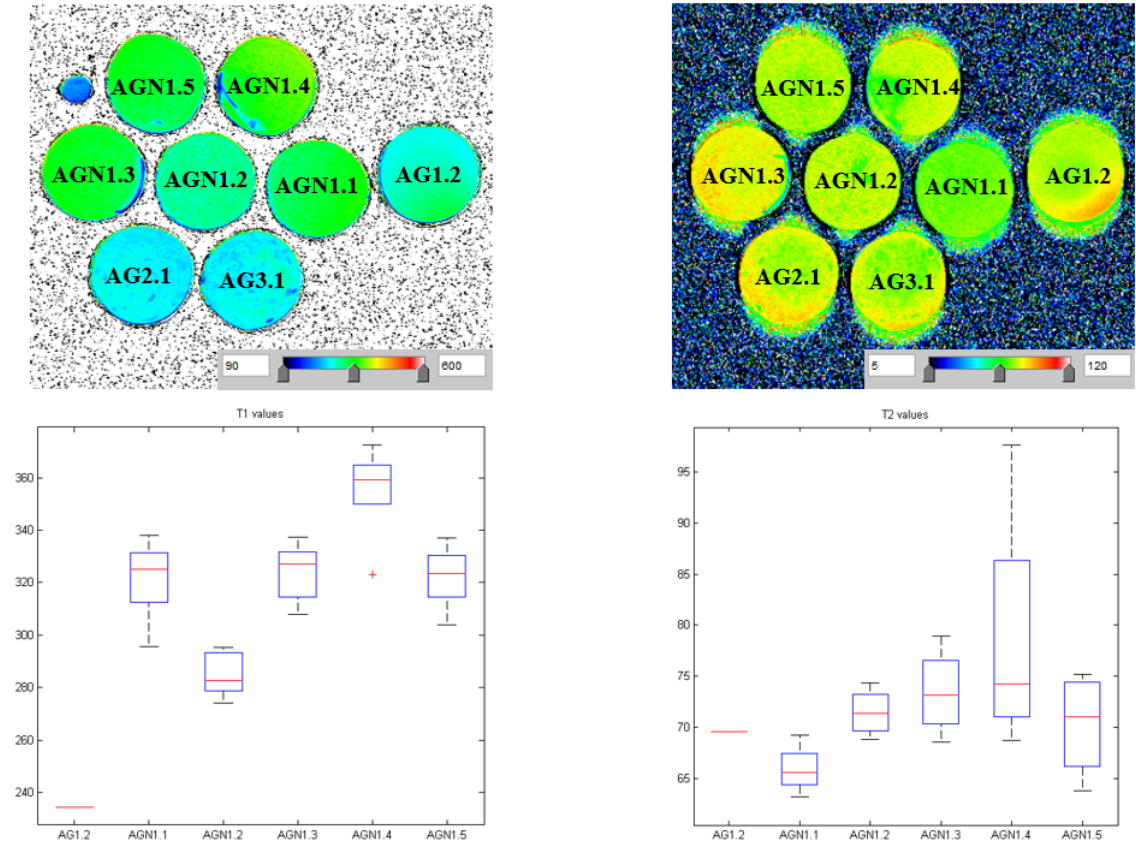


Figure 5.22: T1- (left) and T2-mapping (right) of the AGN samples to assess the influence of N on the relaxation times of tests samples of different initial compositions

¹⁰The mean values for AG1.2 are computed only on the basis of the single image sequence examined, contrarily to the previous set of measures

The influence of C alone is assessed by another series of tests on AG2's set of samples. In this case, the impact of the component appears to be on both relaxation times, T1 and T2. The T1 values are greater than in a C-free sample, and the T2-values are smaller. Increasing concentrations of agarose also reduce the T2 values of a solution so this result appears to be consistent since carrageenan and agarose are two gelling agents that behave practically the same way (see Chapter 4, Section 4). However, deductions from this test set must be considered very carefully since the preparation 2 may lack in homogeneity according to the mapping of AG2.1.

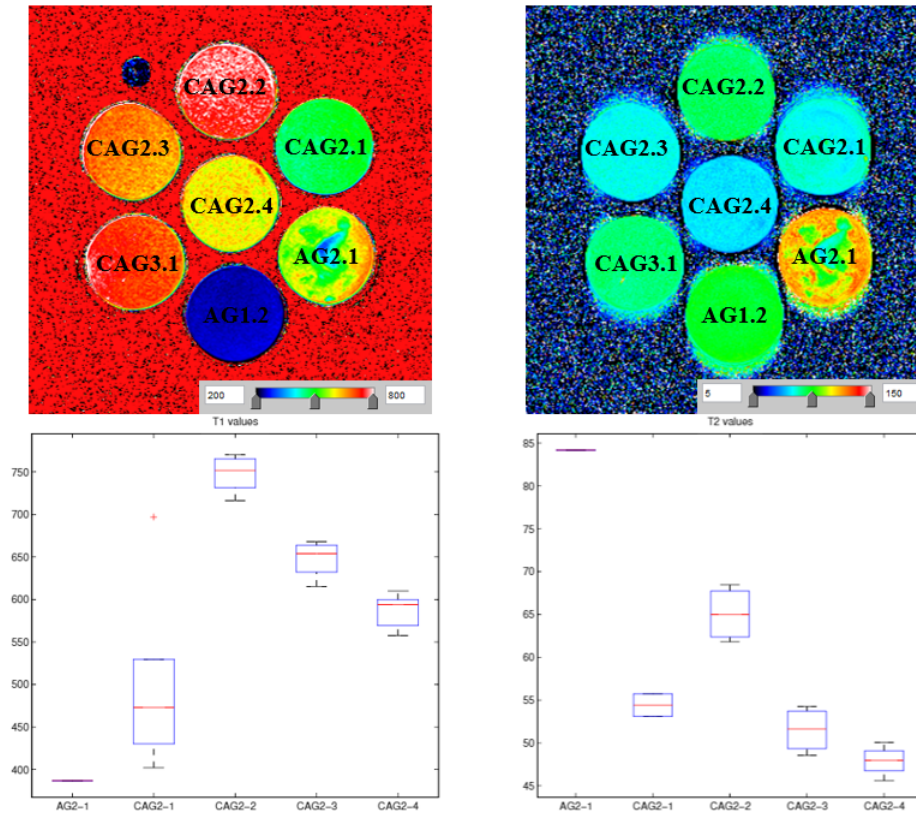


Figure 5.23: T1- (left) and T2-mapping (right) of the CAG samples to assess the influence of C on the relaxation times of tests samples of different initial compositions

The influence of both components, carrageenan and sodium chloride, was then experimented on preparation AG3. An increase of the T1 values of the different samples seems to be clearly correlated to the increasing concentration of carrageenan through the samples, as depicted on Figure 5.24. Each dot (square, circle and diamond) on the diagram corresponds to the mean values of the relaxation times computed within 5 slices of the sample volume. Considering the samples of $N = 0$ (in red) to be outliers, thus not taking them into account in the statistic tests¹¹, the differences between the T1 values of samples of $C = 0.5, 1$ and 1.5 respectively appear to be significant ($p_{value} < 2 * 10^{-4}$ in all cases; $\mu_{0.5} = \mu_{1.0} = \mu_{1.5}$). The T1 values of the composition seem to increase linearly with the increasing concentration of C. However, this assumption must be verified since the pattern is not the same for the 3 samples of AG2 (in red). Regarding T2 values with respect to the varying concentration in C, no conclusion can be derived since the significance level to reject the hypothesis that the averages are equal is not reached ($p_{value} = 0.169$; $\mu_{0.5} = \mu_{1.0} = \mu_{1.5}$). The influence of N on the relaxation times appears to be less clear than for C. Regarding T2 values, the samples with the highest concentrations of sodium chloride have mixed up averages ($\mu = 69.9, 69.5$ and $69.7ms$ resp. for $N = 0.3, 0.4$

¹¹This assumption is not too strong since these samples come from batch 2 whereas the other ones comes from batch III

and 0.5). This is also the case for the two other samples containing sodium chloride ($N = 0.1$ and 0.2), for which it is not allowed to reject the hypothesis that their averages are different ($\mu_{N=0.1} = 70.22ms$ and $\mu_{N=0.2} = 75.5ms$). Once again, the hypothesis that the "red" samples are outliers is considered. Finally, T1 values do not seem to be affected by the variation of NaCl in presence of carrageenan within the compounds on Figure 5.24.

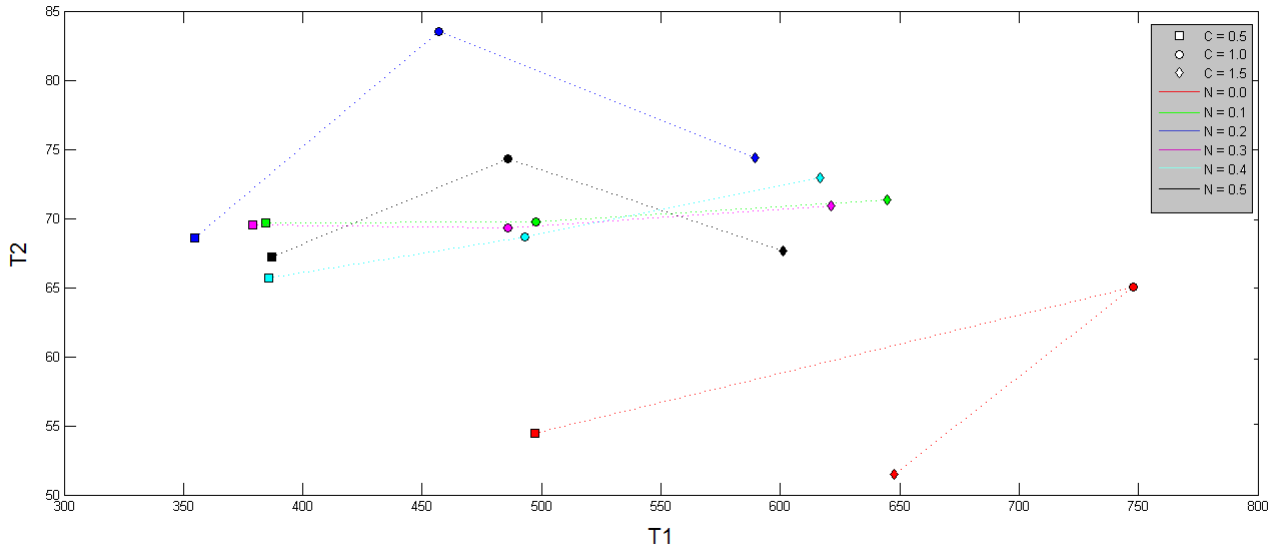


Figure 5.24: Evolution of T1 and T2 with respect to increasing C and N concentrations. Each line connects iso-N samples, each symbol depicts iso-C samples.

An ultimate comparison of the influence of C and N was performed on samples of compositions supposedly close to the ones giving the relaxation times of the pancreas (Figure 5.25). Recall from Chapter 4 Section 4, the relaxation times of the pancreas are 725 ms (T1) and 43ms (T2) respectively. CAGN3.16 should have its relaxation times the closest to these values since it has the composition recommended by Hattori et al. in their publication [58]. The diagrams containing the boxplots seem to favor CAG3.1 as the best candidate to mimic the magnetic properties of the pancreas. We notice that the data for sample AG (agarose-gadolinium-NaN3 without any additional component) are far from the expected values for the pancreas. Moreover, the sample with C only (CAG3.1) has improved results, which demonstrates the non-negligible influence of carrageenan on both relaxation times of the gels. The influence of N in the AGN sample is less marked than for C and than in the previous test (Fig. 5.22). This test suggests that the impact of N and C on the initial AG composition is not simply a cumulative effect of the impact of N and C alone but is rather an intricate combination of the two influences.

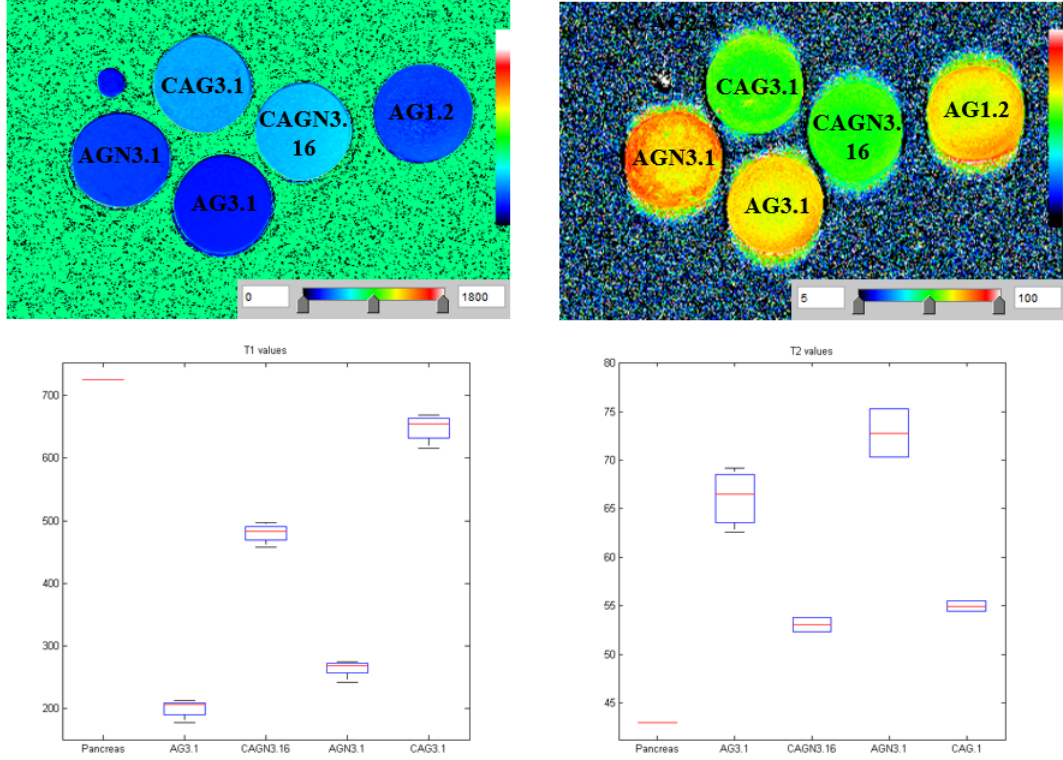


Figure 5.25: T1- (left) and T2-mapping (right) of samples of preparation 3 compared to the relaxation times of a pancreas

3 Achieved objectives

In this section, we will go through the objectives set out in the specifications to review what has been achieved during this master thesis.

MF1 : Mimics the motion of a tumor located in the liver under the influence of the human breathing.

A fake tumor enclosed in a liver-like gel is set in motion by a diaphragm-like membrane activated with a pneumatic circuit. The motion pattern resembles the human breathing cycle with a period of 5.56 ± 0.03 seconds. The amplitude of the motion in the cranio-caudal direction (X-direction) ranges from 12.8mm to 20.1mm. A rotation of about 4° around the sinistro-dexter axis (Y-direction) is observed. The electro-pneumatic regulator of the pneumatic circuit could enhance the amplitudes of motion up to 40mm. However, the technical constraints related to the valve, the input and the output pressures do not allow us to reduce the simulation period and keep a realistic amplitude at the same time (as if the patient was breathing very quickly, due to stress for example).

MF2 : Gives the 3D position of the tumor at all time.

At the beginning of each imaging session, a complete 3D acquisition of the static phantom detects the position of the tumor with respect to the visual tracker on the mold. Thus, by tracking the movement of the mold on which the organs are fixed by rubber bands, it is possible to track the movements of the tumor. Our tracking sequences recorded outside of the MRI chamber ensured that the movements are sufficiently repeatable to give feedback on the position of the tumor along an entire acquisition sequence. Yet, the movements are not reproducible

enough when the phantom is dismantled or moved. Therefore, the calibration at the start of each imaging session is necessary. The tests also revealed that the translation in the sinistro-dexter direction (Y-direction) was negligible. Consequently, only one camera inside the MRI scanner, pointing towards the sagittal view, is sufficient to track the motion of the tumor. With this camera, non-periodic movements are not a problem as a real time tracking is possible.

MF3 : Mimics the contrast values of the upper-abdominal tissues of a human.

The tissue surrogates of the stomach, the pancreas, the liver and its tumor are molded into a gel composed of carrageenan, agarose, gadolinium, sodium chloride, sodium azide, and water (the *CAGN phantom* [48]). The combination of these components allows to produce gels with relaxation times T1 and T2 in the range of the human relaxation times ($T1 = 200\text{-}2000\text{ms}$ and $T2 = 30\text{-}200\text{ms}$). The contrast of the MR image is derived from these T1 and T2 values. Unfortunately, we were not able to replicate the exact T1 and T2 values of the organs of interest in the frame of our master thesis. However, the gels possess sufficiently different magnetic properties to be distinguished from one another on the MR scans.

MF4 : Mimics the mechanical interaction between the organs of the upper-abdominal region of a human.

The liver, stomach and pancreas tissues are mimicked with self-retaining gels. This enabled us to produce organ-like surrogates with realistic shapes. They can be disposed in a mold with the same configuration as in the human body. During the motion, the organs are not compressed as they should but they follow the motion induced by the diaphragm-like membrane to which they are connected. The stiffness of the gels could be improved by varying their composition in agarose and carrageenan but this would impair the T1 and T2 relaxation times.

4 Discussion

After proceeding with tests on the phantom, several aspects are worth discussion. This section is devoted to the remarks, the areas of improvement and the limitations of our prototype.

4.1 Design of the motion mechanism

Our solution was relatively easy to implement.

First, the actuating system : As non-metallic pieces exist for pneumatic circuits, our solution was less trouble than if it was electrically actuated. Then, the sealing of the air compartment of the box was fairly simple because the connections were all static, which would not have been the case if we had to implement a pneumatic piston for example.

However, this system is far from perfect. The main interest of a dynamic phantom is its regularity. Yet, the test results showed that our prototype had to be calibrated whenever it is disassembled. The sources of these motion irregularities are diverse. One of them is the way the mold rests on the box. A first improvement would be to find an MRI-compatible slide system sufficiently effective to eliminate the stick-and-slip phenomenon caused by the friction between the wedge and the box. Still, the relevance of our system of actuation could be questioned in favor of another installation which may be less anatomically accurate but more reliable.

Then, the modularity and the computer control of the electro-pneumatic regulator enabled an accurate and convenient adjustment of the inlet and outlet flow rates and the inhalation and

exhalation times. Nevertheless, the sizing of the valve should be re-evaluated to be able to reduce the breathing period under five seconds.

4.2 Membrane deformation

Another parameter influencing the movement is the way the membrane deforms. Ideally, it should stay vertical at rest and inflate like in the frame 2 of the Figure 5.26. However, since the hydraulic pressure increases linearly in relative to the depth of the box (in blue) and the pressure induced by the compressed air remains constant on the other side of the membrane (in red), the latter deforms as in the frame 1.

This phenomenon is also worsened by the fact that our membrane has been slightly dilated after the first swellings, which prevents it from being stretched and vertical at equilibrium, when the two sides are only subject to atmospheric pressure.

Two ways of managing this phenomenon can be considered : Either make the section of the basin variable in relation to depth to force the hydraulic pressure to be constant. Either to change the properties of the membrane, such as elasticity, as a function of depth.

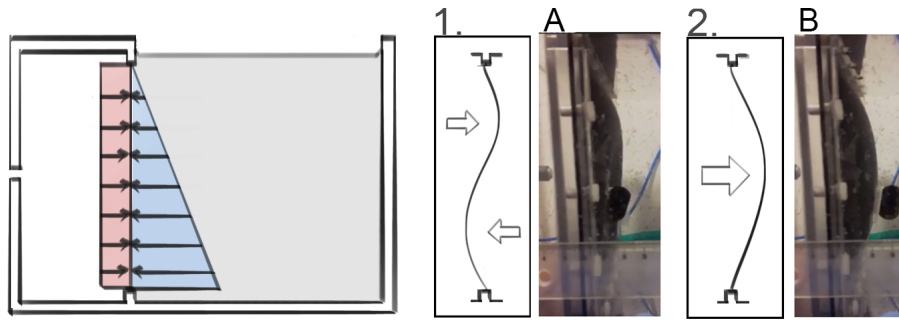


Figure 5.26: Left : Schematic representation of the hydraulic pressure in blue and the compressed air pressure in red. Right : Comparison between pictures and schematic representations of the deformation of the membrane at rest (Frames 1 and A) and when inflated (Frames 2 and B)

4.3 Visual tracking

The first idea was to track directly the tumor inside the liver with a camera placed inside the MRI. Due to the lack of transparency of the organ gels, this idea was adapted. A solution is the use of a visual marker on the mold maintaining the organs together. However, if the real interactions between the organs were simulated, they would deform and the visual tracking would not be relevant anymore.

Moreover, the software used for the video acquisition of the eye-tracking camera seems to have some failures that corrupt the timing of the data. The problem was overcome by a post-treatment of the video, knowing that the respiration cycle was of 5.56 ± 0.03 seconds. In any case, this treatment could be avoided with the use of a robust acquisition software that converts VHS signal to a basic video format (.mp4 or .avi).

4.4 Tissue surrogates

The tissue surrogates have a central place in the implementation of our phantom. The expectations regarding the contrast and the anatomical representation of human organs were high. Despite our low experience in the domain, we did our best to fulfill the corresponding objectives. Our research have led us to choose the *CAGN phantom* [48] to simulate the organs of interest.

This gel-type phantom combines the magnetic properties and dielectric properties essential for the representation of organs in a MRI environment. The dielectric properties of the gels we produced have not been assessed in the frame of this master thesis. However, further studies should inspect the conductivity of the gels to measure the energy loss within the fake organs, and ultimately, within real organs *in vivo*. Though MRI is valued for its low energy transfers to the patient, the length of the examination could have surprising effects on body temperature. Charge displacements also occur when the human body is irradiated with radiofrequency waves. The patient's safety can be severely compromised by this phenomenon and the length of time of the imaging could increase the risks of creating current loops. If the dielectric properties are well defined by the *CAGN phantom*, our phantom could help investigating the phenomena.

In parallel, the effective representation of relaxation times T1 and T2 with the components of the *CAGN phantom* has to be experimented further. In the model described by Kato et al. (2005, [48]) and Hattori et al. (2013, [58]), which is used to evaluate the compositions of the gels given the relaxation rates ($1/T1$ and $1/T2$), carrageenan is not accounted in the equations because its effect is neglected. Yet, our tests suggest that an increasing concentration of carrageenan within the compounds has a significant effect on the T1 values of the preparation. In line with this remark, the influence of sodium azide, the antiseptic, has still not been observed. The importance of this component to avoid seeing the organ-like gels rot has been outlined in this report. Understanding its interactions with the other components of the gel and the hydrogen protons of water could enable to optimize the concentration of this material.

In general matter, the gels should be preserved in better conditions. An optimal quantity of sodium azide would take in charge the rotting issue, but long-term solutions for the dry-up and the erosion of the gels are imperative for a repetitive use of our phantom. In the frame of this master thesis, the organs were enclosed in a food-grade film, which has revealed to be a sufficient way to protect our gels. However, the film tends to slip away and has to be frequently changed. The gel could be wrapped in a conservation film under vacuum to overcome this issue.

Regarding our tracking system, the transparency of the gel could be enhanced. We suggest to decrease the concentration of carrageenan to achieve this but the gel strength is weakened and it could also have some negative effects on the relaxation times of the gel. Other gel types such as silicone gels are completely transparent and could be considered for our application. However, the materials risk to be much more expensive and the gel preparation might be more complex. The gel preparation has already been pointed out as a factor of opacity of the compound in this report because it was not properly handled. Though the procedure is rather simple, many steps cause trouble to be achieved. For the sake of simplifying the gel recipe, alternatives to the heating of the gel could offer better results. In line with this suggestion, the gel could be heated in an oven of controlled temperature rather than in an oil bath to ensure constant temperature throughout the process.

Chapter 6

Conclusion

The objectives of this master thesis were diverse:

First, it was necessary to understand and identify the stakes of MR-guided proton therapy so that the object of our conception was as relevant as possible. Since real-time MR tracking is still under development, the design of a new MRI-compatible mobile phantom is helpful for the tests regarding the choice of the sequence parameters during the mobile image acquisition and of the tumor identification softwares.

Therefore, the second objective of this master thesis was the implementation and manufacturing of this phantom. Its design had to be innovative since phantoms combining, first, the dynamic and anatomical characteristics of the human body and, second, a 3D localization of a tumor inside a moving part of the phantom, do not exist on the market. In spite of the constraints related to MRI, especially concerning magnetic materials, a functional prototype was build. Thanks to an electro-pneumatic system that inflates and deflates an elastic membrane, synthetic organs made of gelatine and contrast agents, bathed in water, are moved according to a controlled respiratory cycle. The main benefits of this design are the ease and cost of its manufacturing, the modularity in the control of the ventilation and the transparency of water and the box which facilitates the tracking.

The third objective developed in this paper was to evaluate the proper functioning of the phantom. Different tests aimed to validate that it was possible to :

- mobilize the organs with a realistic motion. *De facto*, the prototype is capable of performing breathing cycles whose frequencies and amplitudes are credible. However, the device is not steady enough to be used without calibration or real-time tracking inside the MRI.
- mimic the relaxation times T1 and T2 of human organs with gel materials. The obtained values were in the same order of magnitude than human tissues relaxation times but, unfortunately, we could not acquire the exact numbers in the context of our master thesis.
- track in real time the motion inside the MRI-machine. Thanks to the eye-tracking camera inside the MRI, it is possible for us to follow in real time any movements, even the non-periodic ones.

Despite these results, further research has to be carried out regarding :

- the influence of carrageenan and NaCl on the relaxation times T1 and T2 of the tissue surrogates;
- the heat increase of the organs induced by a long-term exposition to RF-radiations during the real-time imaging acquisition;

-
- the resizing of the electro-pneumatic regulator and the diameter of the pneumatic tubes to provide a more reliable solution;
 - the design of the membrane to avoid the s-curved shape at rest;
 - the physical interactions between the different organs inside the body.

To conclude, we can say that, despite a few flaws, this phantom has its place in the development pipeline of MRI-guided proton therapy because it is able to set in motion a surrogate tumor and to track it, both on the MRI acquisitions as well as on an external camera. We also hope that the results developed throughout this master thesis will help to bring the research towards better cancer treatments a little further.

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Appendix A

Nuclear Magnetic Resonance

To understand the magnetic resonance phenomenon, it might be needed to introduce a few concepts from the quantum mechanics of the particles.

Magnetic properties of the nuclei

The nucleus of an atom is constituted of protons and neutrons, thus it is positively charged. In quantum mechanics, this nucleus is characterized by a spin number I . In general, all the particles with an $I \neq 0$ are called "spins". However, in the frame of medical imaging, we are only interested by the hydrogen nucleus (with $I = 1/2$), as it is highly represented in the human body.

The concept of spin can be seen as the rotation of the nucleus on its own axis, just as a spinning top. Due to the positive charge of the nucleus, the rotation motion creates an electrical current and a magnetic field. This magnetic field is characterized by the magnetic moment μ of the nucleus. As a consequence, the nucleus can be described as a little dipole of equivalent μ , like represented in the Figure A.1.

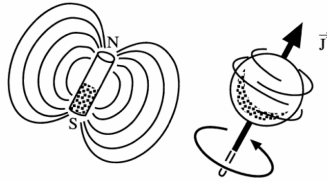


Figure A.1: A nucleus with a rotation motion on its own axis can be represented by a dipole of equivalent magnetic moment μ . [25]

At rest, the magnetic motion has a random orientation. However, when a magnetic field $\mathbf{B}_0 = B_0 \mathbf{I}_z$ is applied, the axis of rotation of the spin tends to align itself with the orientation of the field, either parallel to $\mathbf{B}_0$, or in the opposite direction (antiparallel). This modification of the orientation is due to the interaction between the external field $\mathbf{B}_0$ and the magnetic moment of the nucleus, which creates a torque :

$$\mathbf{C} = \mu \times \mathbf{B}_0 \quad (\text{A.1})$$

Thus, an atom of spin $1/2$ can have two orientations in the field $\mathbf{B}_0$, while a nucleus of $I = 3/4$ could have four different. The Figure A.2 schematizes this concept.

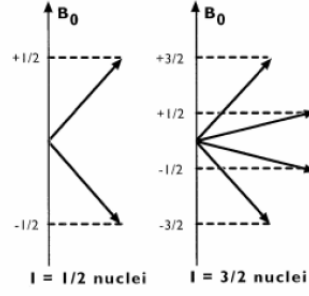


Figure A.2: Schematic of the different possible positions for the magnetic axis of spins $1/2$ and $3/2$. [25]

To continue the analogy of the spinning top wobbling under the effect of Earth's gravity, the spins have a rotation motion that describes a cone around $\mathbf{B}_0$ (see Figure A.3). This motion is called "precession". The rotation speed is proportional to the intensity of the field $\mathbf{B}_0$ and is characterized by the precession frequency or Larmor frequency f_0 :

$$f_0 = \gamma B_0 = \frac{\gamma}{2\pi} B_0, \quad (\text{A.2})$$

with being γ the gyromagnetic ratio, which is a characteristic of the nucleus (e.g. $\gamma = 42.58\text{MHz/T}$ for the hydrogen nucleus).

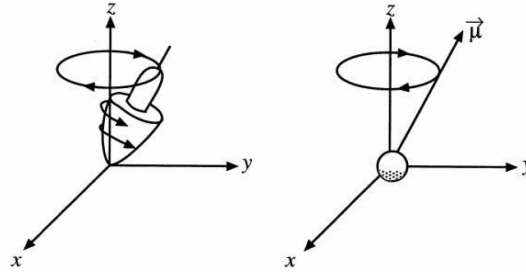


Figure A.3: The oscillation of the magnetic axis of the nuclei inside an external magnetic field is called precession [25]

Appendix B

Needs and requirements

Geelhand Arnould Lechien Vianney Thibaut Tanguy		LIST OF SPECIFICATIONS OF A DYNAMIC PHANTOM COMPATIBLE WITH MRI SIMULATING THE EFFECT OF BREATHING ON THE MOTION OF A TUMOR IN THE ABDOMINAL AREA	DATE: 19/12/2016 VERSION : 3
Context : IBA, world leader in the proton therapy market, wishes to reduce the usage of CT scans through the treatment of cancerous patients. So they created ImagX with searchers from the UCL in order to use MRI technology in their imaging process. As the machine must be calibrated and the treatment lasts long, they need a device that simulates the breathing of a patient and its effect on the motion of a tumor in the abdominal area.			
DATE	ORIGIN	MAIN FUNCTIONS	
26/09/16	Benoit Macq, Damien Dasnoy	MF1 : Mimics the motion of a tumor located in the liver under the influence of the human breathing	
10/11/16	ImagX	MF2 : Gives the 3D position of the tumor at all time	
10/11/16	Benoit Macq, Damien Dasnoy	MF3 : Mimics the contrast values of the upper-abdominal tissues of a human	
10/11/16	Benoit Macq, Damien Dasnoy	MF4 : Mimics the mechanical interaction between the organs of the upper-abdominal region of a human	
		REQUIREMENTS OF MAIN FUNCTIONS	
06/11/16	Students	RMF 1.1 : Reproduce the ventilatory cycle of the reference human* being at rest	
06/11/16	Students	RMF 1.2 : The period of the respiratory cycle is between 4 and 5 seconds	
06/11/16	Students	RMF 1.3 : The amplitude of the diaphragm motion is 2 cm	
06/11/16	Students	RMF 1.4 : Programmable breathing cycle** (frequency, amplitude, pattern)	
06/11/16	Benoit Macq, Damien Dasnoy	RMF 2.1 : Precision of 1 mm (of proton therapy)	
		RMF 3.1 : Distinguish the liver and its tumor, the stomach, the	

06/11/16	Students	upper-part of the colon and the vertebral body RMF 4.1 : Take into account the shape, position and elasticity of the liver and its tumor, the stomach, the upper-part of the colon and the vertebral body
26/09/16 26/09/16 15/03/17 26/09/16 26/09/16 26/09/16 26/09/16	D. Dasnoy Hospitals Hospitals D. Dasnoy D. Dasnoy ImagX ImagX	CONSTRAINTS FUNCTIONS CF1.1 & 2.1 & 3.1 & 4.1 : MRI compatible CF1.2 & 2.2 : Power source CF1.3 & 4.2 : Compressed and vacuum air supply CF1.4 & 2.3 & 3.3 & 4.3 : Life expectancy CF1.5 & 2.4 & 3.4 & 4.4 : Frequency of usage CF1.6 & 2.5 & 3.5 & 4.5 : Budget CF1.7 & 2.6 & 3.6 & 4.6 : Easy to use per one person
06/11/16 06/11/16 06/11/16 06/11/16 06/11/16 26/09/16 15/03/17 06/11/16 06/11/16 26/09/16		REQUIREMENTS OF CONSTRAINTS FUNCTIONS RCF 1.1.1 & 2.1.1 & 3.1.1 & 4.1.1 : For the security, definitions of MRI classification are generally taken from ASTM standard for "Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment", F2503. (http://www.mrisafety.com/TheList_search.asp) RCF 1.1.2 & 2.1.2 & 4.1.2 : Mechanism compatible with the MRI environment RCF 1.1.3 & 2.1.3 & 3.1.3 : The available volume is the one of the MRI environment (inside the MRI device, in the MRI room and outside the MRI room) RCF 1.1.5 & 2.1.5 & 4.1.5: If there is a part of the device outside the room it must be connected through the waveguides of the penetration panel, a 6 cm diameter tube RCF 3.1.4 : The materials must have a similar contrast than human tissues RCF 1.2.1 & 3.2.1 : Standard 220V, 16A available RCF1.3 & 4.2 : 5bar of positive pressure and -0.8bar of negative pressure RCF 1.3.1 & 2.3.1 & 3.3.1 : Life expectancy ⇒ 10 years RCF 1.4.1 & 2.4.1 & 3.4.1 : Frequency of usage ⇒ 1 time/week RCF 1.5.1 & 2.5.1 & 3.5.1 : max 2000€

Appendix C

Morphological Graph

Morphological graph									
PF 1.1 Place	TF 1.1.1 Calibrate phantom position	Alignments lights	Wedge	Laser					
PF 1.2 Configure	TF 1.1.2 Calibrate tumor position	Fixed beacons							
	TF 1.2.1 Set frequency	Programmed by computer	CPU + Memory	Mechanical positions	Pneumatic circuit				
	TF 1.2.2 Set amplitude	Programmed by computer	CPU + Memory	Mechanical positions	Pneumatic circuit				
	TF 1.2.3 Set breathing pattern	Programmed by computer	CPU + Memory	Mechanical positions	Pneumatic circuit				
PF 1.3 Mobilize	TF 1.3.1 Mimic the motion induced by the human breathing on a tumor located in the liver	Balloon	Piston	Piezo-electric motors	Rack & pinion	Crank	Platform	Snake-like robot	Cables
PF 1.4 Track Position	TF 1.3.2 Mimic the influence of the surrounding organs	Foam	Sponge	Real organs	Liquid	Gas	Solid Plates		Cam
	TF 1.4.1 Visualize the Tumor on the MRI scan	Foam	Sponge	Real organs	Liquid	Gas	Solid Ball		
	TF 1.4.2 Visualize the organs on the MRI scan	Foam	Sponge	Real organs	Liquid	Gas			
	TF 1.4.3 Evaluate the position of the Tumor in XYZ with respect to time	Predictable movement	Camera	Strain gauge	Mechanical triangulation	Contact sensors			

Appendix D

Blueprints of the box

Appendix E

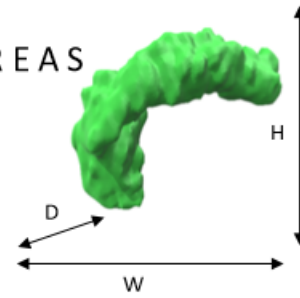
Technical sheets of the tissue surrogates

	Okayama University Gels	Our Gels
C	KC-200S 3% (Mitsubishi Shoji Foodtech Co., Ltd., Tokyo, Japan)	C1013 - suitable for gel prepa 1-3% (Sigma Chemical Corp., St. Louis, MO)
A	Type 1, A-6013 0-1.6% (Sigma Chemical Corp., St. Louis, MO)	Type 1, A-6013 0.6-1.315% (Sigma Chemical Corp., St. Louis, MO)
G	GdCl3 0-140 $\mu\text{mol/kg}$ (Sigma Chemical Corp., St. Louis, MO)	Gd(ClO4)3-hexahydrate 37.5-97.6 $\mu\text{mol/kg}$ (Thermo Fischer Scientific, Lancashire, UK)
N	- 0-0.7% (Katayama Chemicals, Osaka, Japan)	S7653 0-0.371% (Sigma Chemical Corp., St. Louis, MO)
NaN3	- 0.03% (Katayama Chemicals, Osaka, Japan)	S8032 0.03% (Sigma Chemical Corp., St. Louis, MO)
H2O	Distilled	Ultra-pure

Table E.1: Referenced components and their concentrations used to produce CAGN phantoms at the Okayama University (left) [55] and at the Université Catholique de Louvain (right)

TECHNICAL SHEET: PANCREAS

TISSUE CHARACT.:



Mass ¹ kg	Size ²			Relaxation times ³		Dielectric properties ⁴	
	Width cm	Depth cm	Height cm	T1 ms	T2 ms	ϵ' F/m	σ S/m
0.09	10.4	10	9.6	725	43	66.799	0.80407

GEL CHARACT.:

Gel Composition				
Concentrations				
GdCl3 $\mu\text{mol/kg}$	Agarose %	Carr. %	NaCl %	NaN3 %
97.6	1.22	1	0.291	0.03
Quantities (for 1.9kg)				
GdCl3 g	Agarose g	Carr. g	NaCl g	NaN3 g
0.011	2.44	2	0.582	0.06



Gel	Mass g	Size			Relaxation times	
		cm	cm	cm	T1 ms	T2 ms
Gel 1	17.96	1	1	1	458.7	40.5
Gel 2	21.5	1	1	1	/	37

¹doi: 10.1097/PAF.0b013e31823d29ad

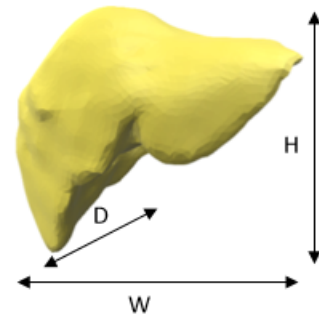
²Patient 5 : <http://www.ircad.fr/fr/recherche/3d-ircadb-01-fr>

³<http://onlinelibrary.wiley.com/doi/10.1118/1.4790023/full>

⁴<http://iopscience.iop.org/article/10.1088/0031-9155/41/11/002/meta>

TECHNICAL SHEET: LIVER

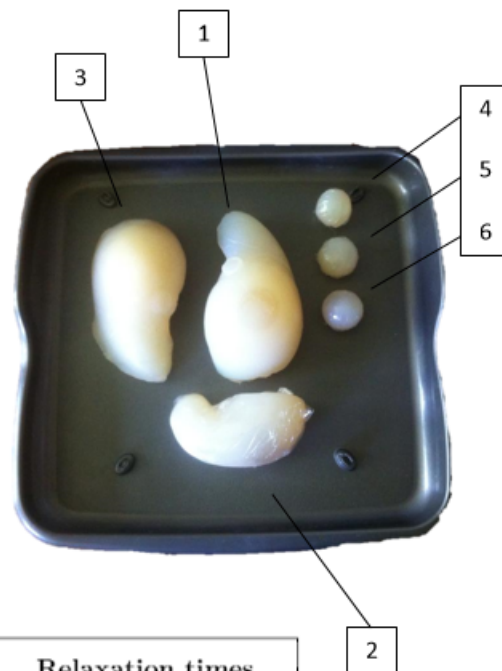
TISSUE CHARACTERISTICS:



Mass ¹	Size ²			Relaxation times ³		Dielectric properties ⁴	
kg	Width cm	Depth cm	Height cm	T1 ms	T2 ms	ϵ' F/m	σ S/m
1.561	20.9	20.8	19.5	812	42	64.286	0.51068

GEL CHARACTERISTICS:

Gel Composition				
Concentrations ⁴				
GdCl3 $\mu\text{mol/kg}$	Agarose %	Carr. %	NaCl %	NaN3 %
82.9	1.315	1.2	0.148	0.03
Quantities (for 1.9kg)				
GdCl3 g	Agarose g	Carr. g	NaCl g	NaN3 g
0.04152121	24.985	22.8	2.7968	0.57



Gel	Mass g	Size			Relaxation times	
		cm	cm	cm	T1 ms	T2 ms
Gel 1	500	1	1	1	/	56.04
Gel 2	197	1	1	1	1212.9 ± 224.9	59.04
Gel 3	371	1	1	1	1271.8 ± 67.9	72.7 ± 3
Gel 4	25.45	1	1	1	/	62.5
Gel 5	22.14	1	1	1	/	66.5
Gel 6	19.36	1	1	1	/	66

¹doi: 10.1097/PAF.0b013e31823d29ad

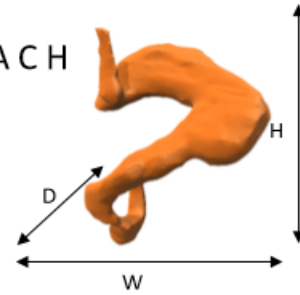
²Patient 5 : <http://www.ircad.fr/fr/recherche/3d-ircadb-01-fr>

³<http://onlinelibrary.wiley.com/doi/10.1118/1.4790023/full>

⁴<http://iopscience.iop.org/article/10.1088/0031-9155/41/11/002/meta>

TECHNICAL SHEET: STOMACH

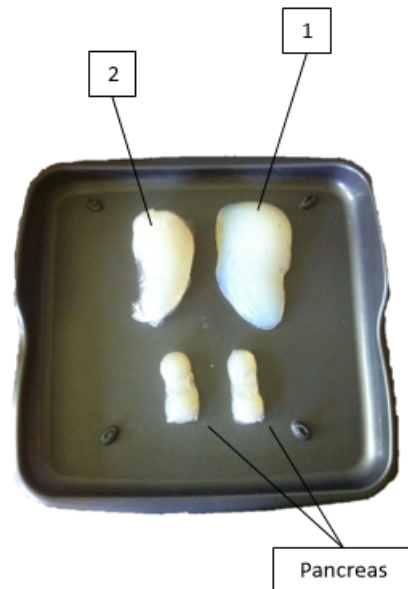
TISSUE CHARACT.:



Mass ¹ kg	Size ²			Relaxation times ³		Dielectric properties ⁴	
	Width cm	Depth cm	Height cm	T1 ms	T2 ms	ϵ' F/m	σ S/m
0.385	15.3	17.6	20.2	1328	61	70.917	0.91269

GEL CHARACT.:

Gel Composition				
Concentrations ⁴				
GdCl3 $\mu\text{mol/kg}$	Agarose %	Carr. %	NaCl %	NaN3 %
34.7	0.895	1	0.371	0.03
Quantities (for 1.9kg)				
GdCl3 g	Agarose g	Carr. g	NaCl g	NaN3 g
0.0136	6.265	7	2.6	0.21



Gel	Mass g	Size			Relaxation times	
		cm	cm	cm	T1 ms	T2 ms
Gel 1	211	1	1	1	/	94.4 ± 2.1
Gel 2	174.34	1	1	1	1660 ± 319.8	82 ± 0.9

¹doi: 10.1097/PAF.0b013e31823d29ad

²Patient 5 : <http://www.ircad.fr/fr/recherche/3d-ircadb-01-fr>

³<http://onlinelibrary.wiley.com/doi/10.1118/1.4790023/full>

⁴<http://iopscience.iop.org/article/10.1088/0031-9155/41/11/002/meta>

Appendix F

Real-time tracking

This appendix presents some extra-data of the tests performed for the motion. The Figure F.1 and F.2 shows the displacement in the X direction (left column) and the rotation around the Y axis (right column) of the organs across the time. These data are extracted from the videos taken with the camera inside the MRI, allowing us to track the marker placed on the mold.

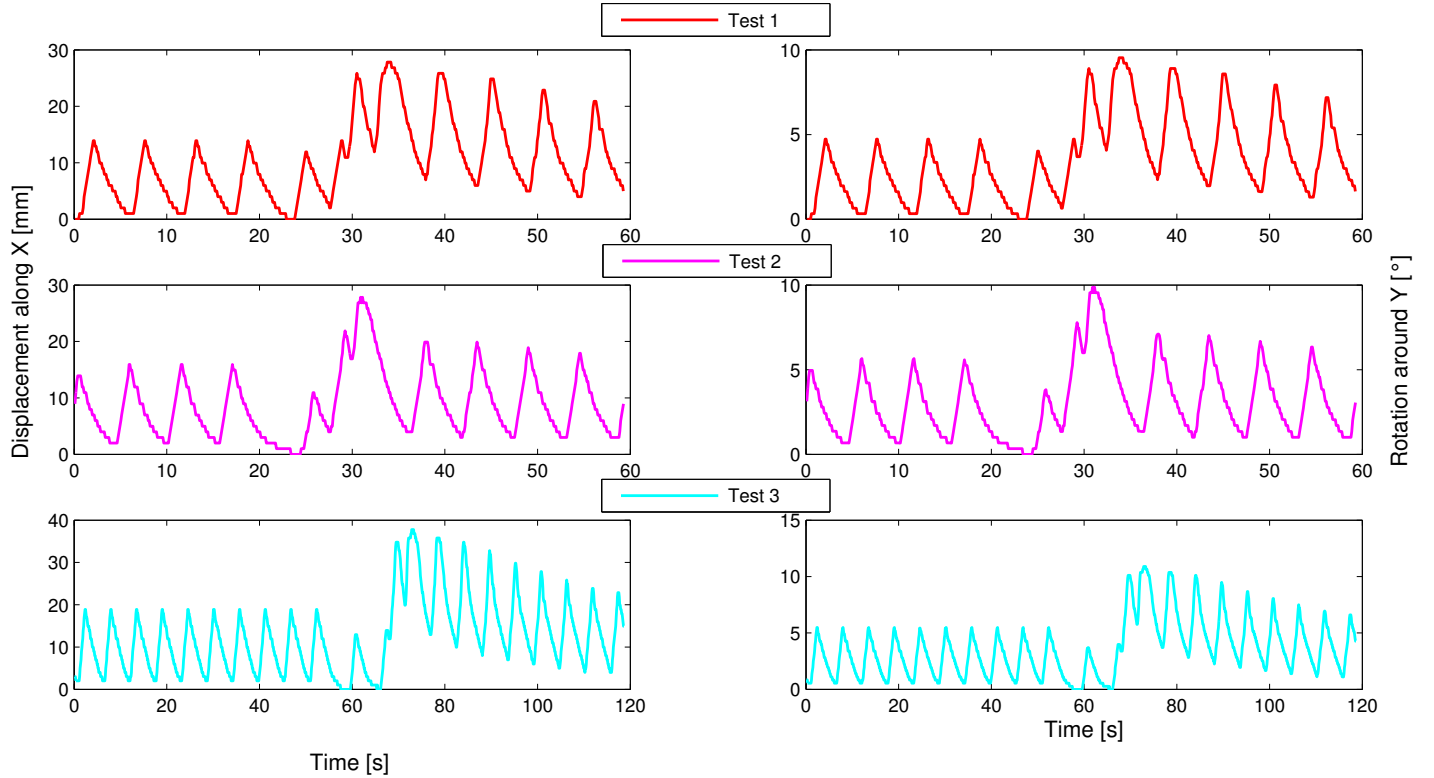


Figure F.1: Translation and rotation of the organs for three tests acquired with the eye-tracking camera inside the MRI

The tests were performed with two respiration patterns : they both start by stable respiration cycles followed by a deep inspiration. In one case, there is a long expiration and, in the second, the cycles continue as before. Other patterns could easily be programmed with the user interface on the computer to mimics the human behaviour.

With these patterns, the amplitude of the inspiration nearly reaches up to 40mm but, in any case, it cannot inflate further more without pressing the organs against the edge of the box.

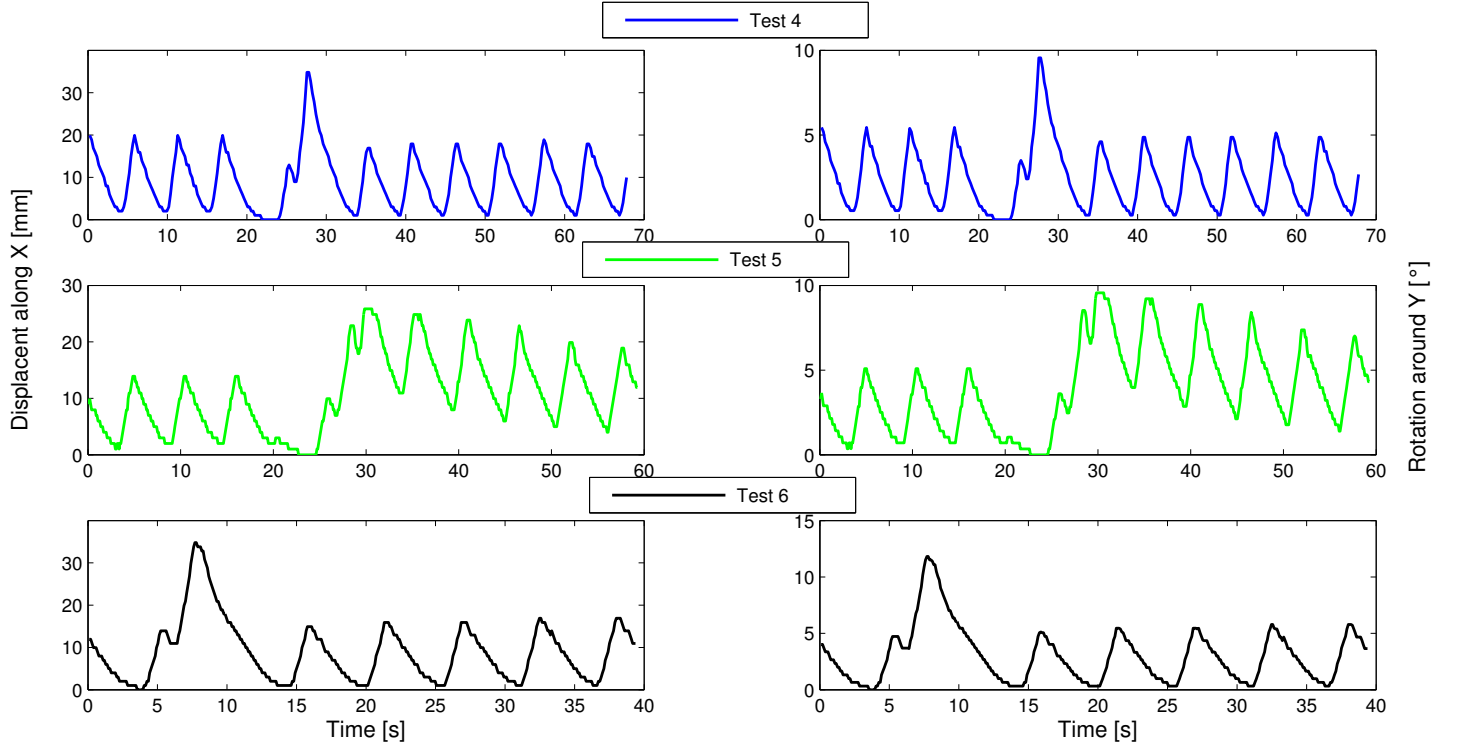


Figure F.2: Translation and rotation of the organs for three other tests acquired with the eye-tracking camera inside the MRI

It is important to notice the test 3, which proves that the system comes back to stable cycles even after a deep inspiration without long expiration. The characteristic time constant is of the order of one minute.

Appendix G

Gel Samples

Composition and relaxation times of the samples derived from Prepa. 1

PREPARATION 1						
Sample	C	N	T1		T2	
	(%)	(%)	(ms)		(ms)	
			μ	SD	μ	SD
AG						
AG1.1	0	0	215.2	11.8	66.2	5.1
AG1.2	0	0	216.2	10	73.7	8.7
AG1.3	0	0	223.1	9.1	68	2.8
AGN						
AGN1.1	0	0.1	321.3	15.9	65.9	2.5
AGN1.2	0	0.2	284.9	8.8	71.5	2.3
AGN1.3	0	0.3	323.7	11.5	73.5	4.3
AGN1.4	0	0.4	355.1	18.7	78.7	12.9
AGN1.5	0	0.5	322.2	12.4	70.3	5.2

Composition and relaxation times of the samples derived from Prepa. 2

PREPARATION 2						
Sample	C	N	T1		T2	
	(%)	(%)	(ms)		(ms)	
			μ	SD	μ	SD
AG						
AG2.1	0	0	386.8	11.4	84.2	15.7
CAG						
CAG2.1	0.5	0	497.1	115.5	54.4	1.8
CAG2.2	1	0	747.7	21.7	65	3.2
CAG2.3	1.5	0	647.5	21.2	51.5	2.6
CAG2.4	2	0	586.2	20.7	47.9	1.8

Composition and relaxation times of the samples derived from
Prepa. 3

PREPARATION 3						
Sample	C	N	T1		T2	
	(%)	(%)	(ms)		(ms)	
			μ	SD	μ	SD
AG						
AG3.1	0	0	206.1	25.9	67.1	3.7
CAG						
CAG3.1	2	0	645.4	101.8	62.4	3.1
AGN						
AGN3.1	0	0.3	264	13.2	72.8	3.5
AGN3.2	0	0.5	/	/	/	/
CAGN						
CAGN3.1	0.5	0.1	384.5	23.1	69.7	2.8
CAGN3.2	0.5	0.2	354.8	13.1	68.6	4.8
CAGN3.3	0.5	0.3	378.9	16.4	69.5	2.1
CAGN3.4	0.5	0.4	385.7	11	65.7	3
CAGN3.5	0.5	0.5	387.1	17.7	67.2	2.9
CAGN3.6	1	0.1	497.5	27	69.7	4.1
CAGN3.7	1	0.2	456.8	15.4	83.5	69.3
CAGN3.8	1	0.3	485.8	12	69.3	2
CAGN3.9	1	0.4	493	17	68.6	3.1
CAGN3.10	1	0.5	486.1	22.4	74.3	4.7
CAGN3.11	1.5	0.1	644.5	19.7	71.4	3.6
CAGN3.12	1.5	0.2	589.4	11.8	74.3	3.9
CAGN3.13	1.5	0.3	621.1	13.8	70.9	3.5
CAGN3.14	1.5	0.4	616.7	22.9	72.9	7
CAGN3.15	1.5	0.5	600.9	20.6	67.6	2.8
CAGN3.16	2	0.3	479.9	16.6	53.1	1

Sketch of the configuration of the samples for the mappings

