Academic Medical Center
Amsterdam

Improving superficial hyperthermia treatment planning

Thesis V1.0

Jort Groen
02-06-2016

Abstract

This thesis discusses the progress made on the development of superficial hyperthermia treatment planning. For superficial hyperthermia treatment, contact flexible microstrip applicators (CFMA) are used. These applicators are bent along the body curvature of the patient. A software tool, written in C++, has been developed for the modelling of CFMA including this curvature and other treatment specific characteristics. The treatment characteristics include variable applicator position, orientation, type, and water bolus thickness. The CFMA is modelled on a segmented patient anatomy, which is acquired from a CT scan of the patient.

Aside from the patient anatomy, the CT scan holds a dummy antenna. From this dummy, CFMA curvature, position and orientation can be estimated/extracted. For modelling of the CFMA, applicator curvature is defined by two separate second-degree polynomial functions. Applicator composition is done by modelling different components independently, which are combined later on. Orientation of the CFMA is established by transforming the segmented patient anatomy, since this is less prone to simulation errors than transforming the applicator, due to possible misplacing of voxels. All treatment specific parameters can be defined/adjusted by the user in a parameter file.

Treatment curvature was investigated and compared to the modelled curvature. Here, an absolute maximum displacement of 1.98 ± 0.99 mm is found, while a test on treatment curvature inter-variance show an average maximum displacement of 6 ± 1.17mm. Therefore, modelling applicator curvature using two separate second-degree polynomial functions is shown an appropriate approach.

Using the developed software tool, treatment specific applicators can now be modelled. Therefore, superficial hyperthermia treatment planning is now complete. In order to further improve superficial hyperthermia treatment planning, the dummy applicator should be adjusted. Furthermore, the ability to model applicators with torsion should be added to the developed tool.

Preface

This thesis was written in the case of a graduation project conducted by Jort Groen, student Mechatronics at The Hague University of Applied Sciences, The Netherlands.

This project was commissioned by the Academic Medical Center, University of Amsterdam, The Netherlands. “The Academic Medical Center (AMC) is one of the foremost research institutions in the Netherlands, as well as one of its largest hospitals. Over 7000 people work here to provide integrated patient care, fundamental and clinical scientific research, and teaching.” (“AMC @ a glance - Academisch Medisch Centrum,” n.d.)

I would like to thank everybody, who in his/her own way contributed to this thesis. In special, I would like to thank my supervisors from the AMC, Petra Kok, Akke Bakker and Hans Crezee, for coaching me, helping me with technical problems and providing support during writing. Furthermore, I would like to thank my supervisor from the Hague University, Rufus Fraanje, for his support during this project.

Table of Contents

Glossary

Active electrode	A conductor through which a current of electricity flows in order to create an electromagnetic field.
Bézier curve	Parametric curve, specified by multiple points within one plane or space.
Cell cycle	Series of events that take place in a cell leading to its division.
CFMA	Contact Flexible Microstrip Applicator, used for superficial hyperthermia treatments.
Complete response	The disappearance of all signs of cancer within the treatment area.
Control	Prolonged complete response.
CT scan	X-ray computed tomography.
Cytotoxicity	Effectiveness against tumour cells.
Dielectric	electrical insulator that can be polarized by an applied electric field.
Disease-free survival	Period of time without return of disease.
Dummy	Fake applicator that is used to simulate the position, orientation and curvature of a CFMA on a CT scan
Fluoroplastic substrate	Part of CFMA.

Hierarchical Data Format file	File format to store and organize large amounts of data.
Hounsfield Units	Unit for tissue density, used in CT.
Hypoxia	Lack of oxigen.
Inter-variance of the applicator curvature	Changes of applicator curvature between treatment sessions within one treatment period.
Newton's systems of equations	Numerical method for solving nonlinear systems of equations.
Overall survival	Survival regardless of disease recurrence.
Parameter file	Text file containing all user defined parameters as input for the software tool.
SAR	Specific Absorption Rate, SAR (W kg^{-1})
Shield electrode	Part of CFMA, conductor used to reflect/steer the electromagnetic field.
Short circuit	Connection between the shield electrode and one of the active electrodes.
Spline	Numerical function that is piecewise-defined by polynomial functions.
Substrate	Part of CFMA between the shield and active electrodes.
The exciting slot	Part of CFMA, Place for excitation of electromagnetic fields.
Treatment period	Period in which multiple treatment sessions are given to a patient.
Treatment response	Effect of treatment on tumour.

1 Introduction

Treatment of malignant tumours includes several techniques. In some cases, surgery alone is sufficient. When surgery cannot be applied or as part of a multidisciplinary approach, radio- and/or chemotherapy can be used. In this case, radio and/or chemotherapy can be applied either prior to, or after surgery. A less widely known treatment modality is hyperthermia. At the AMC, hyperthermia treatments are given as part of a combined treatment modality against cancer.

1.1. Hyperthermia

Hyperthermia, i.e. heating tumour temperature in the range of 40-45°C, is a very effective radiation- and chemosensitizer. The main complimentary effect of hyperthermia on radiotherapy is with regard to DNA damage repair (Kampinga, 2006), cell cycle sensitivity (Westra & Dewey, 1971), and hypoxia (Griffin et al., 2010). Additionally, hyperthermia also causes direct cytotoxicity (van der Zee, 2002). For chemotherapy, the most influential mechanisms for chemosensitation are enhanced DNA damage, an increased intracellular drug uptake, and higher intra-tumour drug concentrations because of an increase in blood flow (van der Zee, 2002).

Over twenty randomized clinical trials showed significant improvement in clinical outcome from hyperthermia in combined treatment with radiation and/or chemotherapy (Kampinga, 2006; Cihoric et al., 2015). Hyperthermia has proven effective in malignant melanoma (2-year control of 46% for irradiation + hyperthermia vs 28% irradiation alone) (Overgaard et al., 1995), bladder cancer (10-year disease-free survival of 53% for thermochemotherapy vs 15% chemotherapy alone) (Colombo et al., 2011), cervical cancer (3-year overall survival 51% for radiotherapy + hyperthermia vs 27% radiotherapy alone) (van der Zee et al., 2000), soft tissue sarcoma (treatment response of 28% chomotherapy + hyperthermia vs 12% chemotherapy alone) (Issels et al., 2010) and recurrent breast cancer (overall complete response of 59% for hyperthermia + irradiation vs 41% irradiation alone) (Vernon et al., 1996).

A hyperthermia treatment consists of multiple treatment sessions equally distributed within a treatment period. Usually a treatment consists of five sessions, given once a week. At the AMC, two types of hyperthermia treatments are given: Deep and superficial hyperthermia. Superficial hyperthermia is practised for tumours up to 4 cm below skin surface. Here, Contact Flexible Microstrip Applicators (CFMA) are applied. A CFMA that, as its name would suggest, can be bent, consists of an antenna, operating at 434 MHz, and a water bolus. The water bolus, located between the antenna and the skin, directs the electromagnetic field from the antenna to the tissue and can also be used to heat or cool the skin. The antenna is used for heating tissue, up to ~4 cm deep. During treatment, the amount of power and the water bolus temperature are adjusted to steer and optimise the treatment. The CFMA is available in five different sizes and can be bent in the direction perpendicular to that of the electromagnetic field in order to fit the curved body contour of the patient.

Jones et al. (2005) showed that variation in thermal dose can result in significant local control difference (2-year survival of 31% for high dose vs 15% for low dose hyperthermia). For example, a too conservative or vigorous approach reduces the effectiveness of hyperthermia (Bruijne et al., 2011). This proves the importance of an adequate treatment steering.

In order to have adequate treatment steering, sufficient (thermometry)data is required of the heat distribution in the patients body during treatment. However, during superficial hyperthermia treatments, thermometry is limited due to a limited number of sensors that incompletely measure the target volume. Because steering is based on the thermometry, this results in lower steering quality and suboptimal heating. For example, at the AMC, multi-element thermocouple strings are used containing 7,14 or 21 sensors per string separated by 0.5 or 1 cm interspace. Here, several thermocouple strings are placed on the patients skin and a few are placed invasively using catheters. This results in around forty measurement points at the skin surface and seven inside the target area. These measurement points mainly shows the heat distribution on the skin surface, but does not give an adequate representation of thermal distribution inside the patient.

A way to obtain more insight in the achieved temperatures in the heated tissue is by simulating the treatment using hyperthermia treatment planning (Kok et al., 2009). The AMC has developed a hyperthermia treatment planning system. The current system consists of an assortment of software tools. Different tools are used for different tasks during the treatment planning process. Planning is done in several steps (also shown in appendix H, Use Case diagram):

- At first, the patient anatomy is modelled. For this, a CT scan is made. On this scan, segmentation of tissue types e.g. bone, fat, muscle, etc. is done, based on the Hounsfield Units of the CT scan. The tumour is outlined manually by a physician.
- Secondly, applicators are modelled at the segmented patient anatomy.
- After this, the electromagnetic field and power distribution is calculated, which is called the Specific Absorption Rate (SAR, W kg^{-1}).
- Based on the SAR distribution, temperature distribution is calculated and visualized.
- Finally, with the visualized temperature distribution of the patient anatomy, treatment can be optimized by adapting power, water bolus temperature, applicator position, applicator orientation, applicator curvature and water bolus thickness.

The AMC currently utilizes the treatment planning system for deep hyperthermia only. Treatment planning for superficial hyperthermia lacks a software tool for the modelling of bent applicators and is therefore not in clinical use. During this project, this tool will be developed to complete superficial hyperthermia treatment planning. Figure 1 shows the build up of hyperthermia treatment planning and the missing tool.

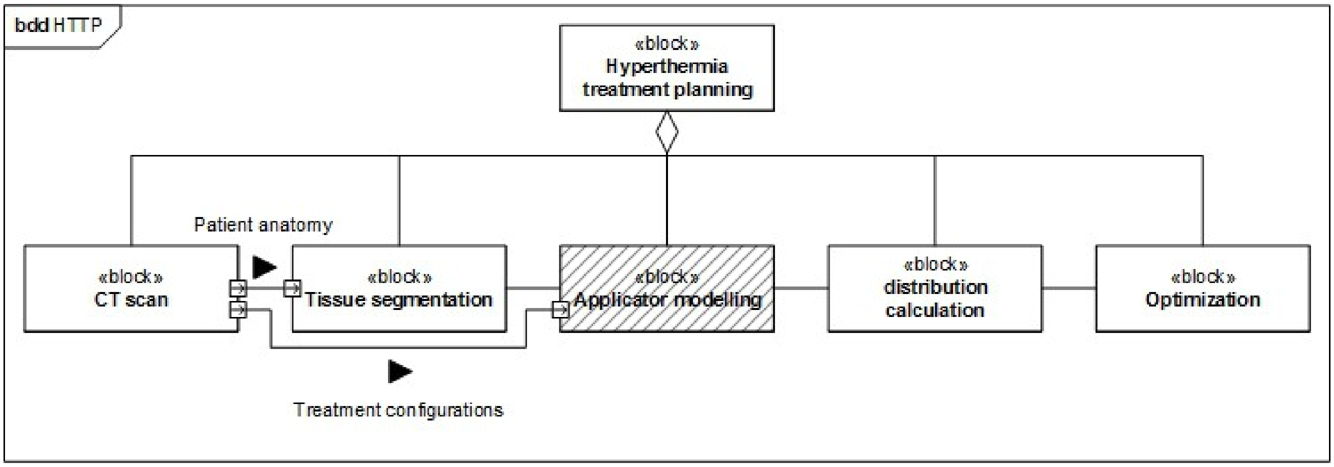


Figure 1: Block definition diagram Hyperthermia Treatment Planning (HTTP)

1.2. Problem definition

Subject of this thesis is the improvement of superficial hyperthermia treatment planning in order to improve clinical outcome of malignant melanoma, soft tissue sarcoma and recurrent breast cancer patients. This thesis was formulated after the research done by Kok et al., (2010) in the development of superficial hyperthermia treatment planning. Kok et al., (2010) concluded that the behaviour of bent CFMA applicators is not trivial and that SAR deposition is not similar for all applicators. During treatment, CFMA are usually bent and the water bolus forms to the patients body, thus varying in thickness per treatment and position. The deformation and size of the antenna, and the thickness of the bolus affects the electromagnetic field distribution of an applicator. Therefore, the applicators need to be modelled treatment specific and cannot be described by a standardized form (Kok et al., 2010).

Kok et al., (2010) showed how to properly model and simulate a CFMA. However, the current approach applies a standardized representation of the CFMA, which is not suitable for clinical practice.

Because of the variance in SAR distribution due to the curvature, definition of treatment curvature is crucial. The current planning systems lacks the ability to define treatment curvature. In order to complement superficial hyperthermia treatment planning, a software tool is required to estimate the treatment curvature. The first goal of this thesis is to develop such a software tool.

Using this curvature, the applicator has to be modelled automatically with the corresponding treatment characteristics (e.g. water bolus thickness and applicator curvature, position and orientation). The applicator needs to be modelled on the segmented patient anatomy, so that simulation can be done. The second goal of this thesis is to expand the software tool for curvature estimation so that treatment specific applicators can be modelled on the segmented patient anatomy.

When this software tool is developed, treatment planning for superficial hyperthermia is complete and can be implemented for clinical use.

1.3. Outline of this thesis

This thesis describes the research performed on superficial hyperthermia treatment planning and the development of a tool for automated applicator modelling.

Chapter 2 discusses the functioning of the software tool. It gives an overview of the inputs and outputs for the system and shows all assumptions made while making this tool.

Chapter 3 addresses modelling of the bent CFMA. At first, in 3.2. the approach for estimating treatment curvature is discussed. Verification of this estimation is also done. Hereafter, the approach for modelling treatment specific CFMA is explained.

Chapter 4 addresses integration of the modelled CFMA into the treatment planning system. This includes rotating and positioning of the modelled CFMA on the segmented patient anatomy. Also, the integration of the parameter file is discussed, used for providing parameters to the tool. Furthermore, the use of the developed software tool is explained.

Chapter 5 enumerates all results of research and development and these are compared to the original requirements.

Chapter 6 draws conclusions and gives recommendations for the improvement of the software tool and the overall hyperthermia treatment planning for the near future.

1.4. Methodology

During this project, the V-model is used. This model describes the different phases which have to be completed to finalize the project. For this project, The last phase: “System Verification and Validation” is inapplicable. The V-model is shown in Figure 2.

In **Concept of operations**, background information and current state of treatment planning is studied. This is done to get a clear understanding of what the project comprehends, and what can be expected. Here, the main goal is defined. Verification and validation of this will not be done within this project. This phase is addressed in Chapter 1.

In the **Requirements and Architecture** phase, detailed requirements are stated, which should be met by the system and architectural models are made. In order to verify and validate the system, the software tool is tested for different curvatures and applicators in the Integration, test, and verification phase. Because the developed software tool is a standalone tool, the complete treatment planning is not tested. These phase elements are discussed in Chapter 2.

During **detailed design**, an approach to examine and model treatment curvature is developed. This curvature is verified on a real applicator with treatment curvature. Also, a technique to model the applicator is developed. This is tested by modeling different curvatures during implementation. This phase is described Chapter 3.

In **Integration, Test, and Verification phase**, The software is tested on the requirements. When needed, adjustments are made and tested until the software tool satisfies to all requirements. This phase comprehends Chapter 4 and 5.

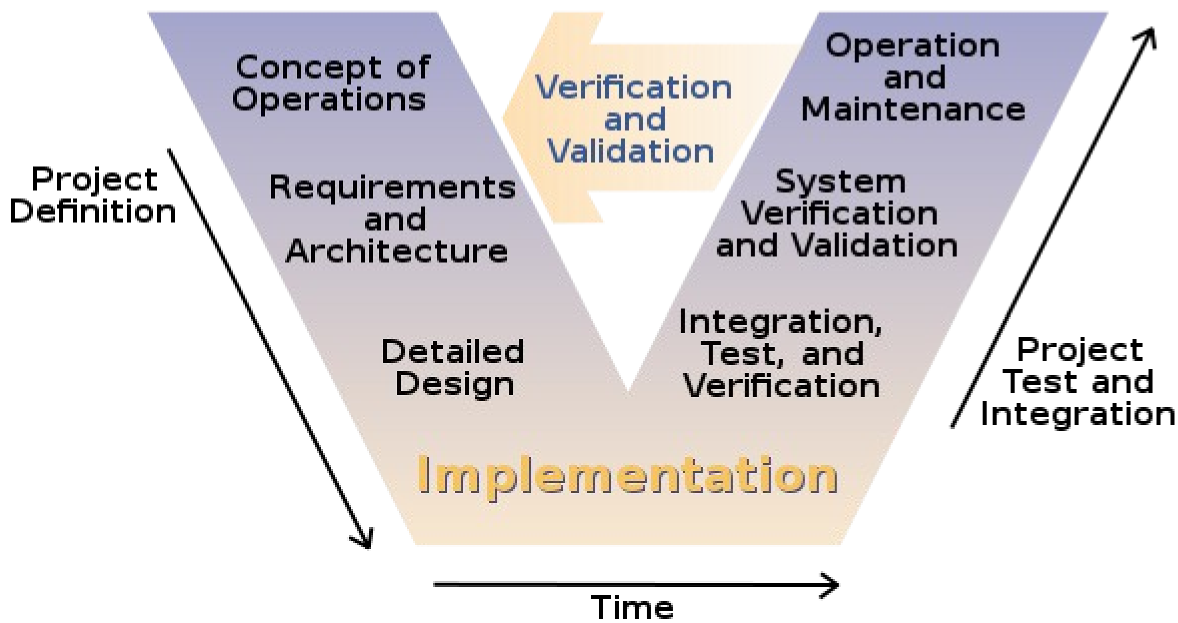


Figure 2: V-model (“V-model - Wikipedia,”)

2 Input, output and assumptions

For the software tool to be complete, it has to give an output so that simulations can be made. The tool will need input data to accomplish this. Processing the input and developing the tool requires some background assumptions. Figure 3 shows a visualisation of the input and output system.

Figure 3: Input output modelling tool

2.1. Input

The following input will be available for the tool.

- CT scan;

  A CT scan is available for each patient. It contains one or two dummy antennae which are placed in treatment position and orientation. The CT scan is stored in a Hierarchical Data Format file.

- Segmented patient anatomy;

  On the segmented patient anatomy, the applicator has to be modelled. The segmented patient anatomy is stored in a Hierarchical Data Format file.

- User input.

  If necessary, user input can be used e.g. applicator type, water bolus thickness. However, to pursue a user-friendly tool, the amount of user input should be limited.

2.2. Output

The tool has one single output. A file containing a modeled CFMA on the segmented patient anatomy. The CFMA includes all treatment characteristics. For compatibility with the other treatment planning tools, the output file is in Hierarchical Data Format, which is supported by the other planning tools.

Treatment characteristics are:

- Applicator curvature: the estimated treatment curvature of a CFMA;
- Water bolus thickness;
- Applicator type;
- Applicator position;
- Applicator orientation.

All requirements for the output can be found in appendix B, User requirements and appendix C, System requirements.

2.3. Assumptions

- CT scan is perfect. The CT scan coordinates are exact.
- The segmented patient anatomy is based on the same CT as the input CT scan.
- The dummy antenna has the same dimensions as the treatment applicator.
- Bending of CFMA is only done around the axis perpendicular to the electromagnetic field.
- The applicator is not bent more than 180º.
- All applicators can be modelled as described in Kok et al. (2010).

3 Modelling bent CFMA

Some CFMA have a fixed curvature, others are curved treatment specific. When a CFMA is bent during treatment, it is bent by hand until the applicator fits the curvature of a patients body. Because of the variance in the human body contour, applicators are not always symmetrically bent.

3.1. CFMA design

There are five different CFMA sizes. Depending on the target area(s), different types or different combinations of types are chosen. The five types are: 1H, 2H, 3H, 4H, 5H. Next to the five flexible applicators, there are also applicators with a fixed shape, recognisable by the “A” in front of the applicator name. A photograph of three CFMAs is shown in figure 4. Figure 5 shows the dimensions of the 2H, 3H, 4H and 5H applicators (1H is missing).

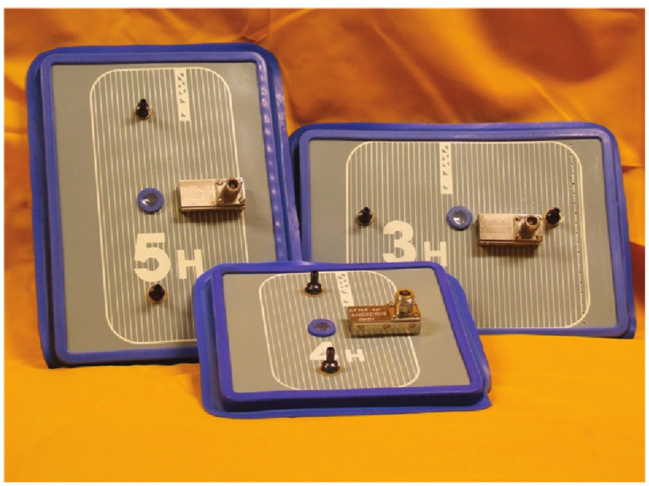


Figure 4: Photograph of the 3H, 4H and the 5H applicator (Kok et al., 2010)

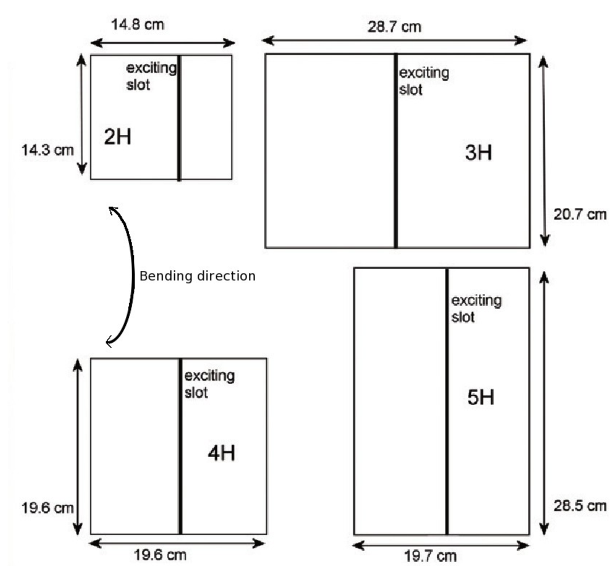


Figure 5: CFMA Dimensions (Kok et al., 2010)

The direction of the electromagnetic field is perpendicular to the lines on the surface of the applicator, which can be seen in Bending is only possible along these surface lines (can be seen in Figure 4). corresponds to the axis perpendicular to the exciting slot (figure 6, B) (Kok et al., 2010). A CFMA consists of two coplanar active electrodes and a shield electrode, separated by a layer of fluoroplastic substrate. The electrodes are excited as a plane dipole-like microstrip antenna by means of a slot of approximately 5 mm. The microstrip line is excited by the feeding pin of a coaxial cable. A short circuit is positioned at approximately $\frac{1}{4}\lambda_s$ from the exciting slot, where λ_s is the wavelength of the field in the fluoroplastic substrate (~44 cm). A rubber frame is mounted around the electrode plates. Within this frame, a water bolus is located. To prevent collapse of the water bolus, rubber lugs are placed at the antenna side oriented inwards. Figure 6 shows a schematic picture of the CFMA applicator.

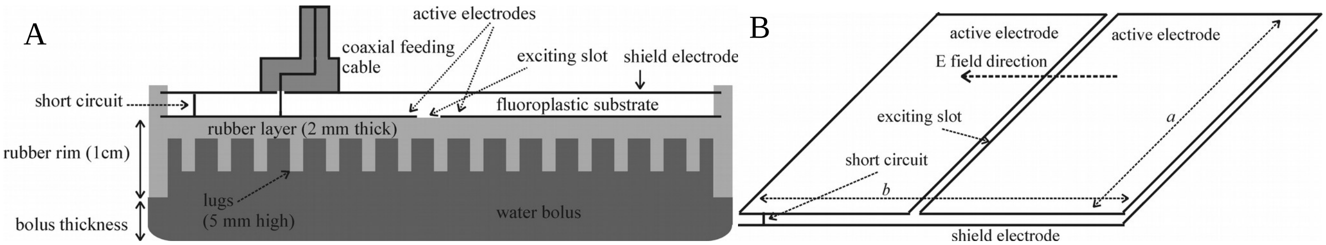


Figure 6: Schematic drawing of a CFMA (Kok et al., 2010)

Kok et al., (2010) showed that a CFMA can be modelled as illustrated in figure 7 and figure 8.

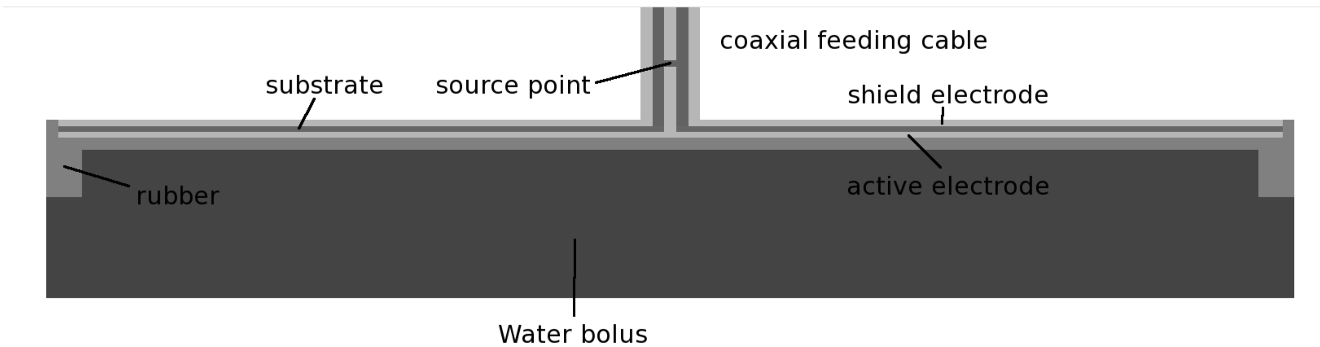


Figure 7: CFMA cross section parallel to the exciting slot

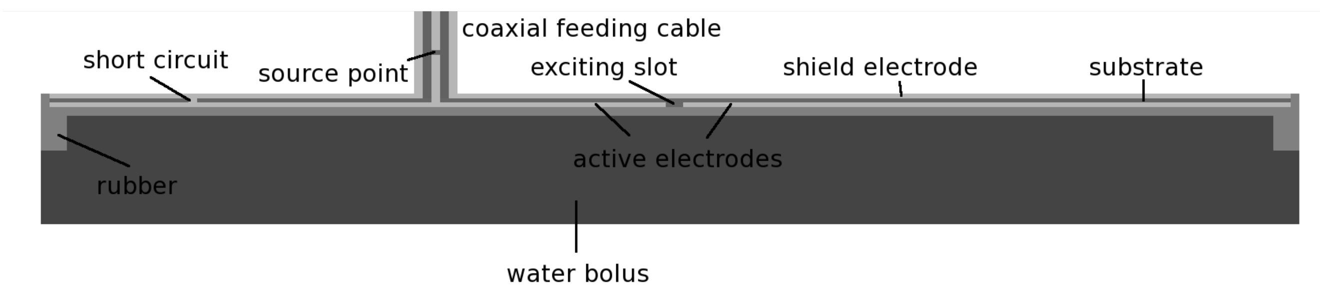


Figure 8: CFMA cross section perpendicular to the exciting slot

3.2. Applicator curvature estimation

For the modelling of bent CFMA, the curvature introduced by the bending of the applicator plays a major role. This is for the reason that nearly all different components have this curvature implemented. Therefore, at first, treatment curvature was analysed, after which an appropriate method for the modelling of this curvature can be developed. Using this method, the different components containing this curvature can be modelled. The Figure 9, 10 and 11 represent a common treatment curvature.

Figure 9: A 2H applicator (fixed curvature) without rubber

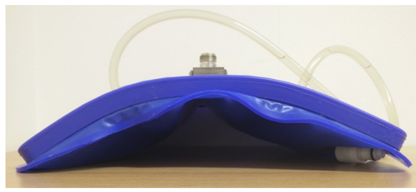


Figure 10: 5H applicator with treatment curvature

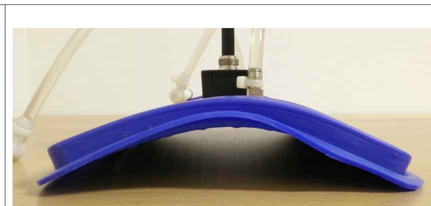


Figure 11: 3H applicator with treatment curvature

During treatment, applicators are bent until they fit around the body contour of the patient. As can be seen in figure 9, 10 and 11, applicators follow a smooth curvature with limited amount of bendings[1] (one or two bendings). Although the curvature looks homogeneous, the curvature seems to vary between treatments. However, due to the positioning of the connectors, the applicator is always flat at the centre of the curve. Also noticeable is that the areas with the strongest changes in slope are near the flat centre. This gives the following criteria for the curvature to be modelled:

- The curve has to be a smooth/organic shape;
- The curve can have two or more bendings;
- The centre of the curve has a slope approximating zero;
- The areas with the strongest changes in slope are near the flat centre.

The applicator curvature, as well as its orientation and position, can be based on a CT scan of the patient (figure 12). However, because of the interference of metal components from inside the CFMA with the imaging radiation, the CFMA cannot be scanned. Therefore, dummy antennae are used. The dummy antennae are composed of different materials and therefore do not interfere with the imaging radiation. They are placed on the patient similar to the corresponding CFMA during the treatment. As result, treatment position, orientation and curvature can be estimated using these dummy antennae.

1 Times the operator bends the applicator for a treatment.

For the estimation of the curvature, it has to be taken into account that the stiffness of the dummy does not exactly correspond to that of the applicators. The reconstruction of the applicator position, orientation and curvature will be addressed in Section 4.1.

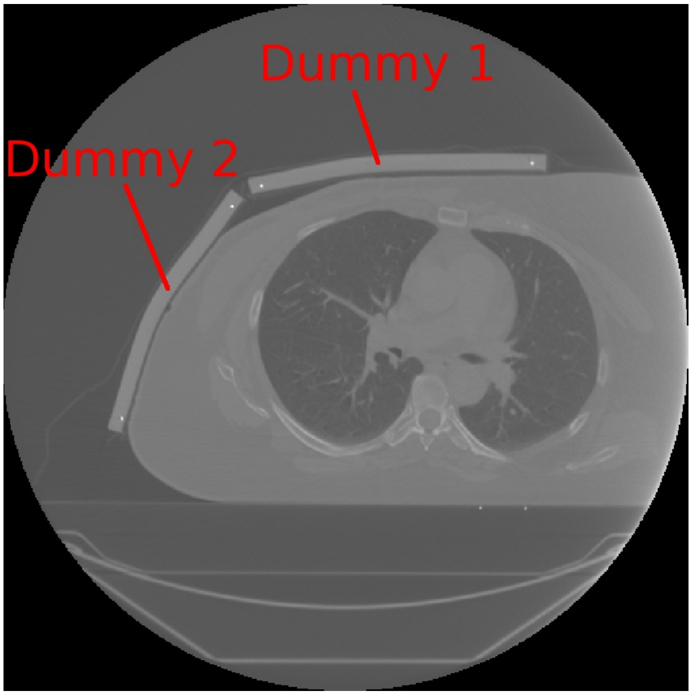


Figure 12: Example of CT scan containing dummy antennae.

Because applicators are treatment specifically bent, a method to establish various different curvatures has to be chosen/developed.

The following methods can be used to establish the shape of an antenna:

1. Feature recognition;
   A) Outline of the dummy applicator;
   B) Patient body contour.
2. Using existing tools;
   A) Ellipse fit;
   B) Rotated ellipse.
3. Line trough predefined points.
   A) Point to point straight;
   B) Point to point curve fit.

1A, Outline of the dummy applicator:

Since the dummy applicator approximates the real CFMA curvature, the shape of the dummy can be adopted. Here the outline can be used as base for the CFMA to be modelled. A disadvantage is that the dummy can also be bent along the direction of the electromagnetic field. This deformation is not allowed for real CFMA and therefore results in an unrealistic curvature. Furthermore, the dummy is less rigid than the actual applicator and therefore more bent which also results in a less realistic curvature. Although establishing the curvature solely using the outline of the dummy may not be optimal, the dummy can also be used for different techniques e.g. determining points used in approach 2 or 3.

1B, Patient body contour:

During treatment, CFMA will be bent following the body contour of the patient. Therefore modelling an applicator according to body contour could be conceivable. However, more than the dummy, the contour will result in deformation along the direction of the electromagnetic field and thus results in less realistic curvature. Figure 13 shows an example of an applicator not following the patients body. Therefore modelling a CFMA that always follows body contour, is not realistic.

2A, Ellipse fit:

The treatment planning system provides tools to create cylindrical and elliptical objects. These functions could be used to model an applicator. The advantage with respect to approach 1 is that the ellipse will only have curvature around the desired axis. The disadvantage is that only one bending can be modelled. Another disadvantage is that the ellipse shows a strong curvature near the outer ends of the curve. This phenomenon is not desirable.

2B, Rotated ellipse:

As variation on 2A, the ellipse can be rotated so that the curve's slope is more homogeneous distributed. However, this approach has the same disadvantages as 2A. Furthermore, the symmetry within the ellipse is a disadvantage. This symmetry rarely occurs in the shape of an applicator and is therefore not representative for all applicators.

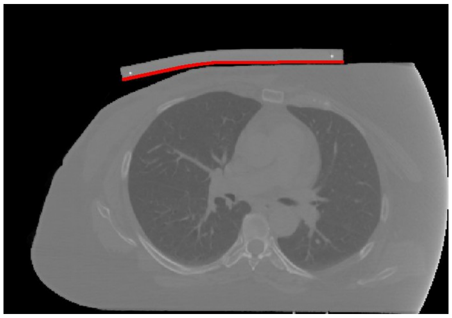
3A, Point to point:

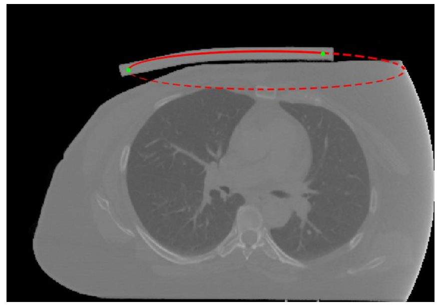
Although using the exact contour of the dummy may be a too excessive approach, the dummy can be used to define points on which treatment curvature could be based. An example is shown in figure 14, 3A, where the curvature is based on three points estimated from the dummy antenna. Although the position of the points can be acquired accurately, the curvature does not follow a smooth/organic shape. This is a disadvantage. In order to get a more fluent curvature, more points need to be defined.

3B, Point to point curve fit:
Another option to get a more smooth shape using the predefined points, is by fitting a function through these points. For example an exponential, hyperbolic or polynomial function.

These methods including the variations are shown in Figure 14. Each approach has its own advantages and disadvantages. These advantages and disadvantages are shown in table 1.

Figure 13: Superficial hyperthermia treatment with an applicator not following body contour

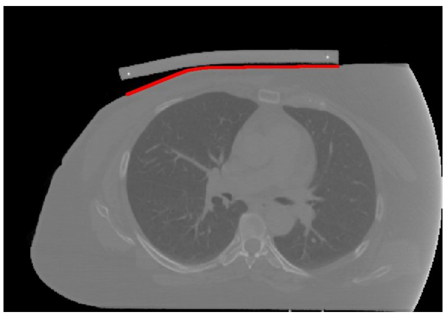


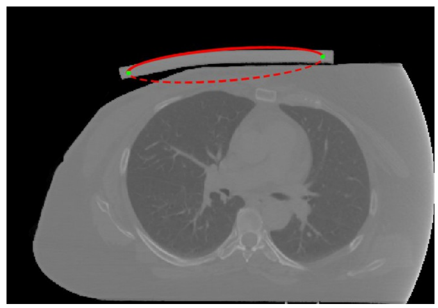


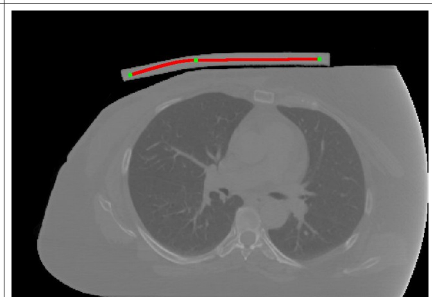
1A. Outline dummy

2A. Ellipse

3A. Point to point straight







1B. Outline patient

2B. Rotated ellipse (3pnts).

3B. Point to point curve fit

Figure 14: Possible approaches

	1A	1B	2A	2B	3A	3B
The curve has to be a smooth/organic shape	+	-	+	+	-	+
The curve can have at least two deformations	+	+	-	-	+	+
The centre of the curve has a slope approximating zero	-	-	-	-	+	+
The deformations are located near the centre or spread equally	+	-	-	-	-	+

Table 1: Approach comparison

As can be seen in table 14, 3B, using predefined points with a function fit seems to be the preferable method.

For function fitting trough the points, several functions could be used to describe the curve. Parabola, polynomials, bézier curve, spline, and other methods/functions were tested. Since the slope of the curve at the centre approximates zero, the curve can there be divided into two separated parts, each defined by its own function. After visualising the different methods and fitting them on the applicator curvature, describing the curve by two separate second order polynomial turned out to fit best, while still simple to define. Validation of this approach is done in Section 16.

3.2.1 Modelling the curvature

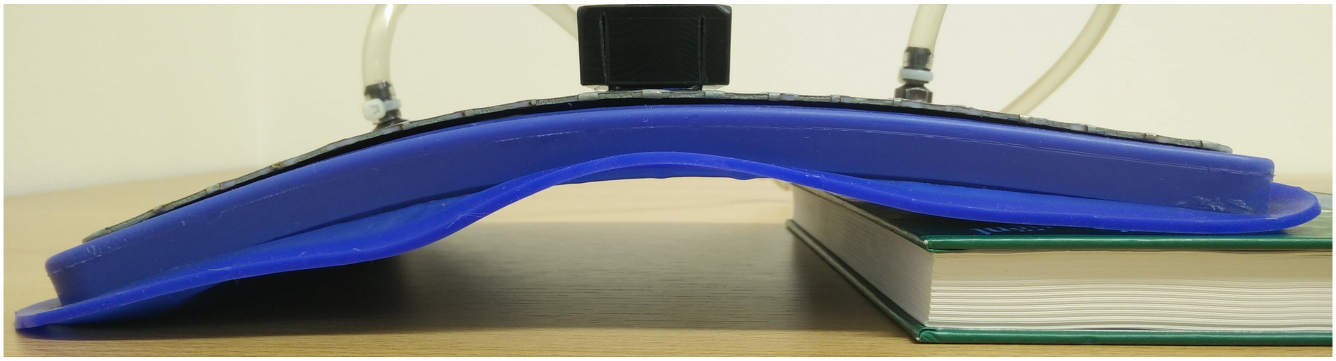


Figure 15: Applicator curvature

In figure 15, a treatment curvature of a 5H applicator is shown. Here, the antenna is lifted from the rubber frame to get a clear view of its shape.

The curvature can be divided into two segments: A left and right side, defined by three points (P1, P2 and P3). The curvatures and their points including world coordinates (coordinates measured inside the real world) are drawn in figure 16. The functions for describing the curvature are based on these points.

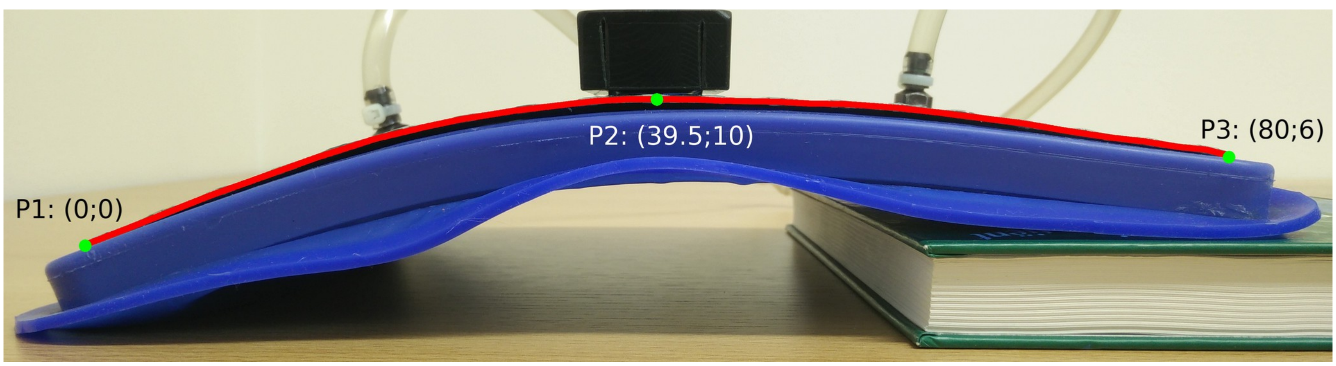


Figure 16: Applicator curvatures defined by three points including world coordinates (in mm)

$$P_1 = \begin{bmatrix} x_1 \\ y_1 \end{bmatrix} \quad P_2 = \begin{bmatrix} x_2 \\ y_2 \end{bmatrix} \quad P_3 = \begin{bmatrix} x_3 \\ y_3 \end{bmatrix}$$

The standard form of a polynomial function is $y = f(x) = Ax^2 + Bx + C$. Here A, B, and C are unknown and need to be determined. When dividing the curvature into a left and right side, the following functions are acquired:

$$y[P1,P2]=f(x)=A_L x^2+B_L x+C_L \quad , \quad y[P2,P3]=f(x)=A_R x^2+B_R x+C_R$$

Where L is for left side variables and R is for the right side variables. In order to compose each function, three equations are needed. However, because the curvature is divided into two separate parts, there are only two defined points per side and thus two equations per function. Therefore, because of the slope approximating zero at the centre of the curvature, the third equation $f'(x_{P2})=0$ is introduced. Where $f'(x)=2Ax+B$. With substitution, the following equations can be subtracted:

- $$A=\frac{\mathrm{P2}_y-\mathrm{P1}_y}{\mathrm{P2}_x{}^2+\mathrm{P1}_x{}^2-2(\mathrm{P2}_x\mathrm{P1}_x)} \qquad (1)$$
- $$B=2A\,\mathrm{P2}_x \qquad (2)$$
- $$C=\mathrm{P1}_y+A\,\mathrm{P1}_x^2-B\,\mathrm{P1}_x \qquad (3)$$

In order to compose the function for the right side, P1 has to be replaced by P2, and P2 has to be replaced by P3.

After the functions are created, the curve can be drawn. This is done by following the function for the left side from P1 to P2, and following the right side function from P2 to P3. In figure 17, a modelled curve is shown which corresponds to the applicator shown at figure 15.

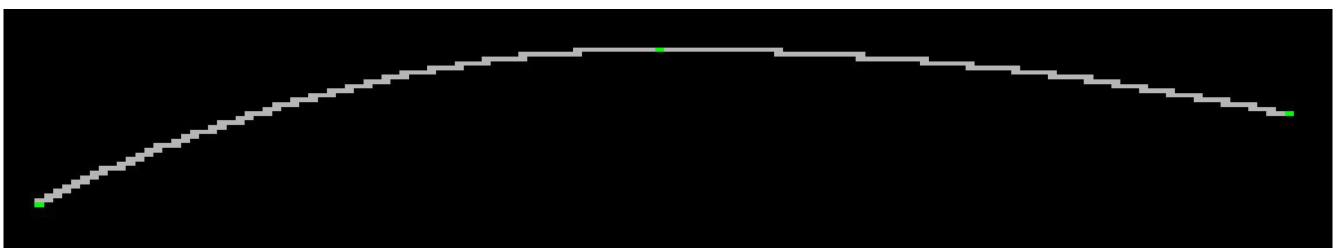


Figure 17: Modelled curvature

3.2.2 Validation of the curvature

In order to know whether modelling the curvature with two second order polynomial functions is an appropriate way, modelled curvatures were compared to treatment curvatures. Both the fixed curved applicators and bendable applicators containing treatment curvature were examined (eight in total). This procedure including measurement results can be found in appendix D, Estimated applicator curvature measurements. Results of the examination are shown in figure 18.

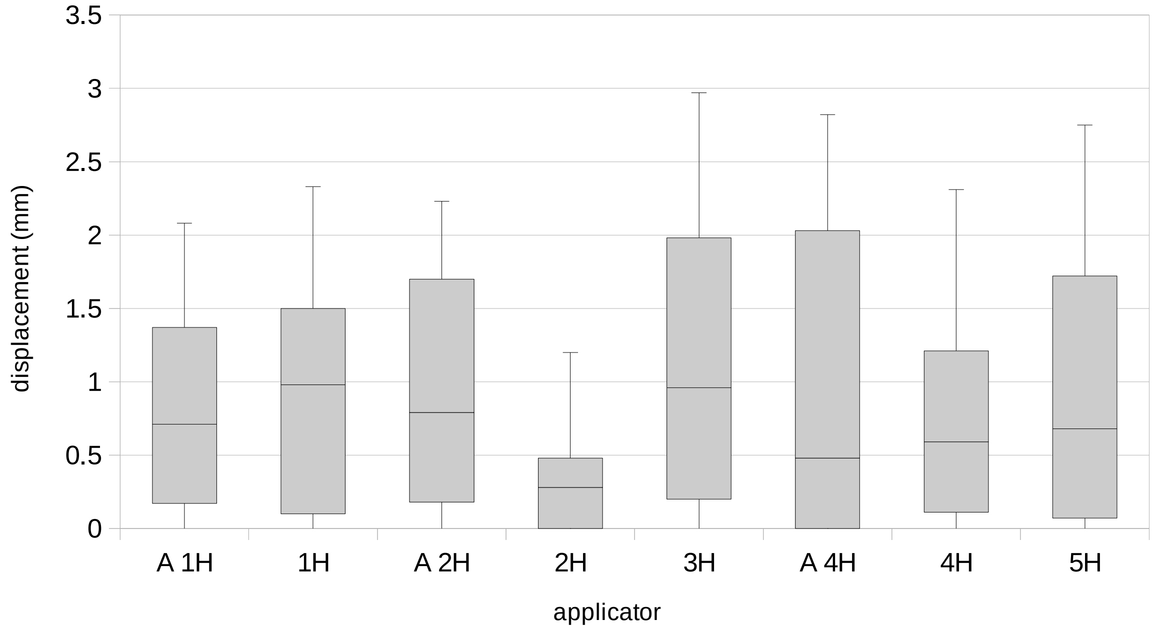


Figure 18: Function curvature displacement per applicator. The applicators A 1H, A 2H and A 4H are applicators with a fixed curve.

Here, the maximum displacement is about 2 mm. To determine whether this is sufficient, the displacement can be compared to the inter-variance of the applicator curvature within a treatment period. Measurements of the inter-variance of applicator curvature within a treatment period can be found in appendix E, CFMA treatment curvature inter-variance.

The inter-variance applicator curvature measurement showed a mean maximum variance of 6 ±1.17 mm. This, compared to the function curvature displacement of maximal 1.98 ±0.99 mm shows that two second order polynomial functions adequately describe applicator curvature.

3.3. Curvature recognition

To compose the two functions corresponding to a curvature, the starting point (P1), centre point (P2) and end point (P3) are required. When looking at a patient CT scan that includes a dummy, the coordinates of P1 and P3 can be easily determined (Figure 19). The location of P2 is harder to determine. Dummy stiffness correction could be done by shifting P1 and P3.

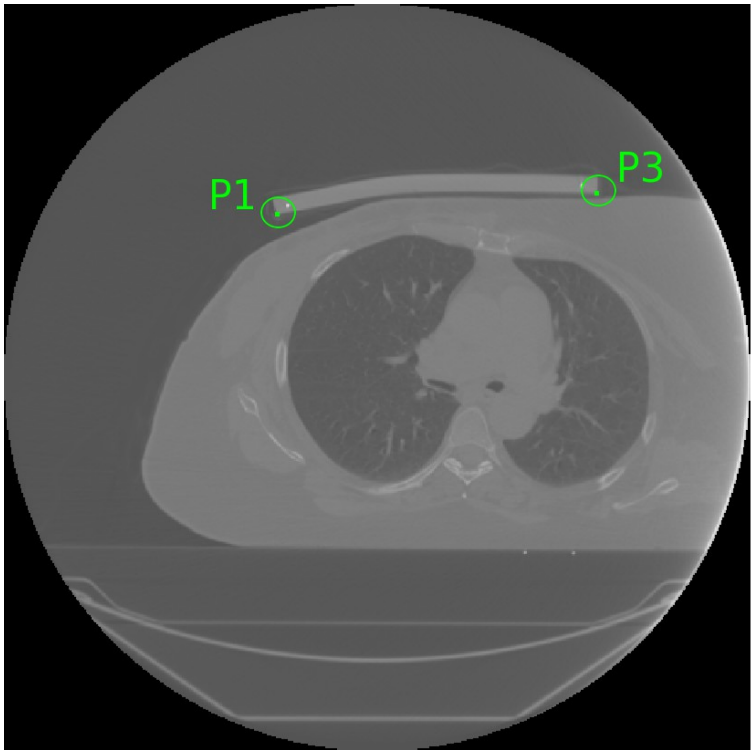


Figure 19: Determination of P1 and P3 on a patient CT

Choosing P2 incorrectly can result in incorrect dimensions of the modelled applicator. Also, estimating both $P2_x$ and $P2_y$ introduces uncertainties which may be significant for the simulation. Therefore, an additional method is developed using applicator length. This way, only one of $P2_x$ or $P2_y$ needs to be estimated. Furthermore, the use of this additional method can make future optimisation and/or automation simpler.

When $P2_x$ or $P2_y$ are not determined, there will be three equations and four unknowns, which is under-determined and cannot be solved. Therefore, a fourth equation is introduced:

$$\int_{P1_x}^{P2_x} \sqrt{1+f'(x)^2}\,dx = l_{P1P2} \tag{4}$$

Where l_{P1P2} is half of the length of the applicator, which is known. This function basically states that the travelled distance from P1 to P2 on function f(x), should be equal to half of the applicator length since P2 is located at the centre of the curve. This equation can also be applied for the right half, where P1 has to be replaced by P2, and P2 has to be replaced by P3.

The elaboration of equation 4 for $f(x)=Ax^2+Bx+C$ is:

$$\int dl \;=\; \frac{-(B-2Ax)\sqrt{(B-2Ax)^2+1}+\operatorname{arsinh}(B-2Ax)}{4A}+constant$$

Where $constant=\frac{-B\sqrt{B^2+1}+\operatorname{arsinh}(B)}{4A}$ because at $x=0$ the travelled distance $\int dl$ equals zero.

Together with equations 1, 2 and 3, this gives a system of five non-linear equations:

- $0 \;=\; -A\,\mathrm{P1}_x^2+B\,\mathrm{P1}_x+C-\mathrm{P1}_y$
- $0 \;=\; -A\,\mathrm{P2}_x^2+B\,\mathrm{P2}_x+C-\mathrm{P2}_y$
- $0 \;=\; -2A\,\mathrm{P2}_x+B$
- $0 \;=\; \frac{-\sqrt{(B-2A\,\mathrm{P2}_x)^2+1}\cdot(B-2A\,\mathrm{P2}_x)+\operatorname{arsinh}(B-2A\,\mathrm{P2}_x)}{4A}+constant-l_{P1P2}$
- $0 \;=\; \frac{-B\sqrt{B^2+1}+\operatorname{arsinh}(B)}{4A}-constant$

Where A, B, C, $\mathrm{P2}_y$ and *constant* are unknown. In order to solve this system of non-linear equations, Newton's method for systems of equations is used. For implementation of Newton's method, the opensource “eigen library” for C++ is used for the linear algebra.

3.4. Constructing the bent applicator model

When the curvature is determined and single curves can be modelled, the applicator can be assembled. The applicator is drawn in eight different layers:

1. The water bolus;
2. The rubber frame;
3. The active electrodes
4. The shield electrode;
5. The fluoroplastic substrate;
6. The short circuit;
7. The exciting slot;
8. the Coaxial feeding cable.

The locations of all layers are shown in figure 7 and 8. An overview of the composition of all layers can be found in appendix G, Internal Block Diagram Applicator modelling.

A fully modelled curved CFMA is shown in figure 20. Different layers correspond to different components and thus different materials. For the simulation to distinguish between the different materials, each material is given its individual index, in figure 20 displayed as a different shade of grey. Some layers are thicker than others. For example, the water bolus has bigger dimensions than the electrodes. Most layers follow the specified curvature and are therefore drawn following the two composed functions. Thicker layers are acquired by repeatedly redrawing the curvature on top of each other.

When drawing the CFMA, later drawn layers may overwrite previous ones. In some cases, this results in undesired artefacts e.g. short circuit and holes/gaps. Therefore, the order of assembly is of importance. After all layers are drawn, the CFMA is complete. An overview of the modelling steps taken within the software can be found in appendix F, Activity diagram. At first, it opens the parameter file and imports all parameters. After this, the orientation and positioning is done, addressed in Section 4.1. Finally, the software models the CFMA.

Figure 20: Modelled CFMA front view

3.4.1 Water bolus

The water bolus is the largest component of the CFMA. Its standard size is one centimetre but can be adjusted using the parameter file, a text file used for providing parameters to the modelling tool. The size of the bolus also adapts to the resolution of the CT scan. Figure 21 shows an example of a modelled water bolus.

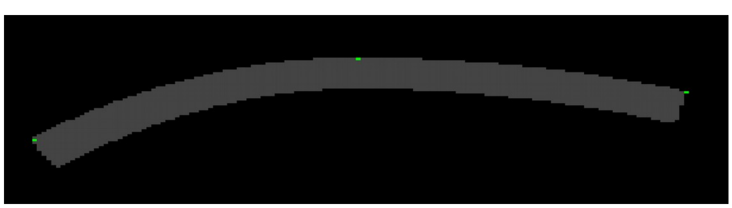


Figure 21: Modelled water bolus

Note that the left and right side edges of the water bolus are perpendicular to the curvature. In order to establish this, a linear path is made on which P1 and P3 are shifted.

To ensure contact with the patients anatomy, the bolus is drawn bigger and prior to the patient. As result of the patient partially overlapping the water bolus, the water bolus is nicely fitted around the patient.

3.4.2 Rubber frame

The rubber frame consists of two parts: the body and the rims. The body is drawn as a curve. The rubber rims are drawn perpendicular to the curvature. The thickness of the body, rims and the extend of the rims are determined by the resolution of the CT scan. A modelled rubber frame is shown in figure 22.

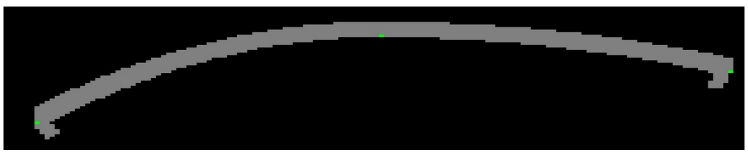


Figure 22: Modelled Rubber frame

3.4.3 Electrodes

There are three electrodes per applicator. The left and right active electrodes, and the shield electrode. The left and right electrodes are modelled as one electrode at first, but is divided into two when drawing the exciting slot, which overwrites the layer partly. The shield electrode is drawn above the active electrodes, separated by the spacing of a substrate layer. Because the thickness of an electrode is smaller than the resolution of the CT, it is modelled as a one voxel curve since this is the minimum achievable. It is of importance that the electrode's voxels are adjacent to each other, so there will be no gaps during simulation. However, voxels corresponding to the active electrodes may not be adjacent to the shield electrode, for this will cause short circuit during simulation. In figure 23 the modelled electrodes are shown.

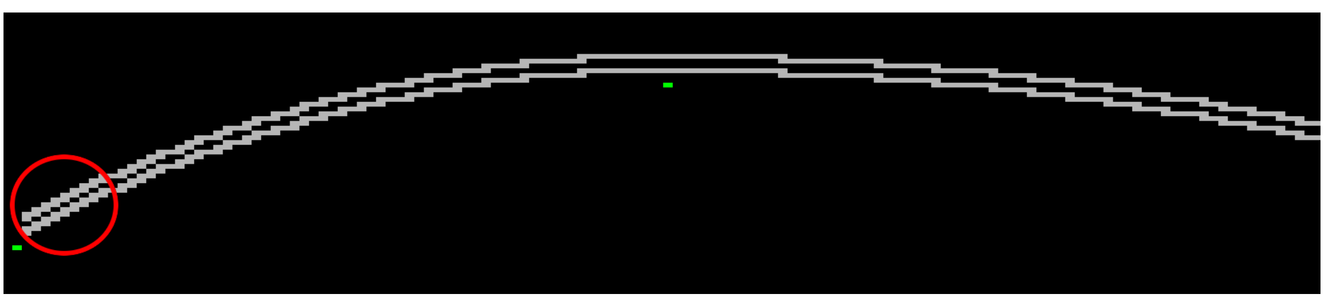


Figure 23: Modelled electrodes

Note that in figure 23, there is short circuit on the left half of the curvature. This will be fixed by overlaying the substrate.

3.4.4 Fluoroplastic substrate

Between the active electrodes and the shield electrode, a substrate layer is placed. Like the water bolus and the rubber frame, its thickness adapts to the resolution of the CT scan. By placing the substrate layer after the electrodes, the substrate will hereby partly overwrite the electrodes and thereby prevents short circuit. However, this introduces the probability of creating gaps into the electrodes. Therefore, a gap-finding-and-fixing algorithm is written. This algorithm analyses during drawing whether each drawn substrate voxel is surrounded by an other substrate voxel or an electrode voxel. If this is not the case, the algorithm draws the missing electrode voxels.

A modelled substrate layer is displayed in figure 24.

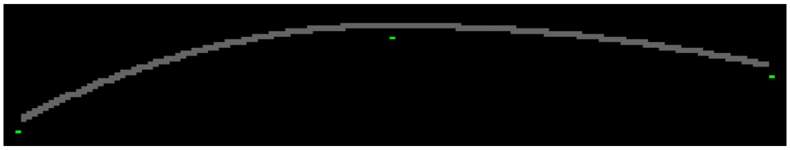


Figure 24: Modelled substrate

3.4.5 Short circuit

The short circuit connects the active and the passive electrodes. The location is indicated in figure 25. Except for its index and length, the short circuit is identical to the substrate layer. Its index is similar to the electrode's. The short circuit length and position is applicator specific. For this length, the short circuit completely replaces the substrate.

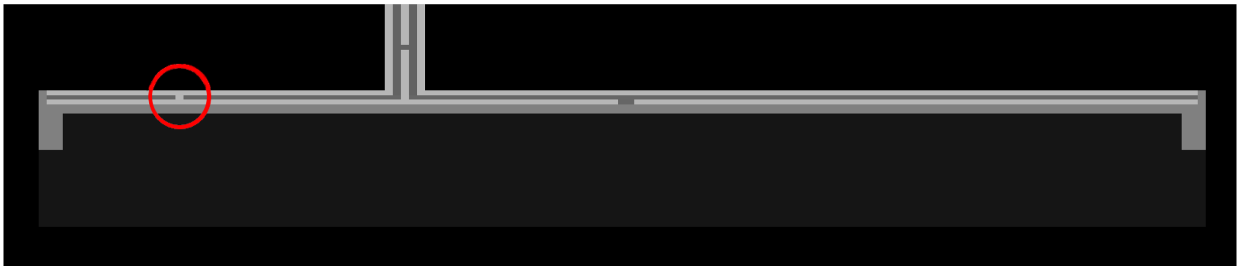


Figure 25: Short circuit side view

3.4.6 Exciting slot

The exciting slot partially replaces the active electrodes. The exciting slot is indicated in Figure 26. The position and length of the exciting slot is depending on the CFMA type. The exciting slot is made out of fluoroplastic substrate and therefore has the same index.

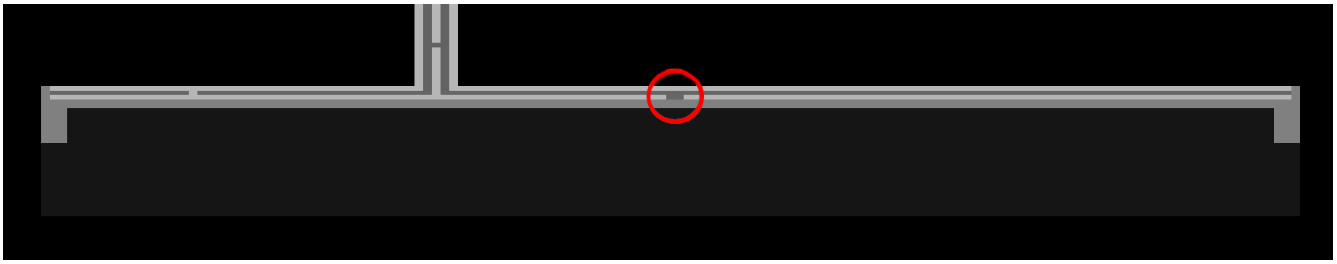


Figure 26: Exciting slot side view

3.4.7 Coaxial feeding cable

The final component is the coaxial feeding cable. This cylindrical cable consists of an outer and inner conductor, separated by a dielectric. The dielectric and outer conductor are shorter so that these layers better integrate into the existing modelled applicator. The coaxial feeding cable is shown in figure 27 and 28.

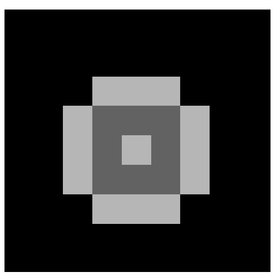


Figure 27: Coaxial feeding cable top view

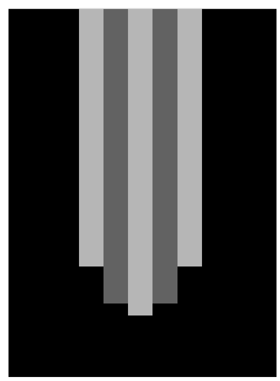


Figure 28: Modelled coaxial feeding cable

The position of the feeding cable is applicator dependent. As result of strong curvature, the placing of the cable may result in undesirable artefacts such as gaps, short circuit or a poor connection. To counter these artefacts, a repairing algorithm was developed. At first, the coaxial cable was drawn with each component index slightly different than the required index. This way, the repairing algorithm can distinguish between the original applicator and the feeding cable. The repairing algorithm then inspects the active electrodes, fluoroplastic substrate and the rubber frame for inappropriate voxels belonging to the cable and heals them.

4 Integration in treatment planning

For the software tool to fit in the current planning, the applicator not only has to be modelled, but it also needs to be placed on the segmented patient anatomy. This should be done on the right position with the corresponding orientation. The applicator has six degrees of freedom: three translations and three rotations. The parameters for these transformations are based on the dummy antenna from the CT scan.

The treatment specific characteristics i.e. applicator type, water bolus size, applicator curvature, applicator position and applicator orientation are based on user input and are provided to the program through the use of a parameter file. Although the providing applicator type and bolus size is pretty straightforward, defining sufficient data for the tool to reconstruct applicator curvature, position and orientation is more demanding. For this, in order to pursue a user-friendly tool, the amount of user input is limited to the definition of six points from the CT, which can easily be determined.

4.1. Applicator position and orientation

The user has to define six points on which applicator curvature, position and orientation will be based. These points should correspond with the outer edges of the dummy antenna as can be seen in Figure 29 and 30 and can be extracted from the CT scan.

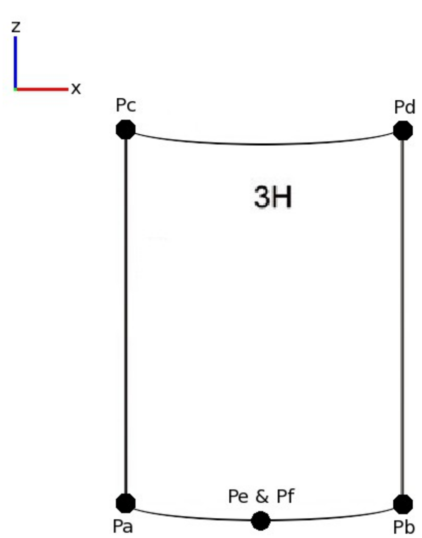


Figure 29: Marked outer points of a 3H applicator top view

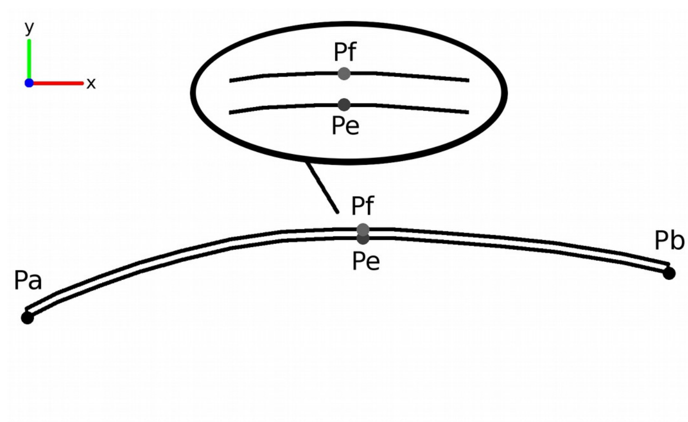


Figure 30: Marked outer points on curvature of 3H applicator front view

The points Pa, Pe and Pb in Figure 29 and 30 correspond to the in Section 10 discussed P1, P2 and P3. These points are used for the curvature recognition.

The extraction of the outer points is done manually using a visualisation tool available in the treatment planning system, which shows three cross sections at any selected point. At this point, the cross sections give the sagittal, coronal and transversal view (Figure 31). In Figure 32, 33 and 34, a transverse, coronal and sagittal view is shown. Here, the outer points of the dummy are marked black. Using this tool, world coordinates of the outer points can easily be determined.

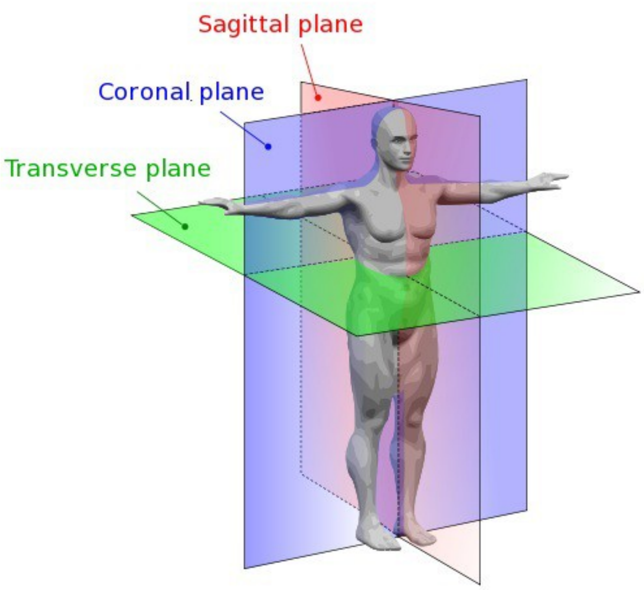


Figure 31: anatomical planes (Gvs14, 2012)

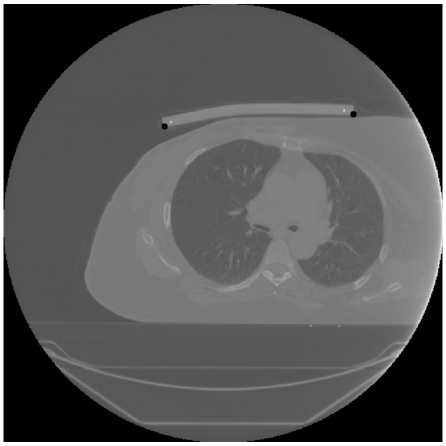


Figure 32: CT scan transverse plane, outer points marked

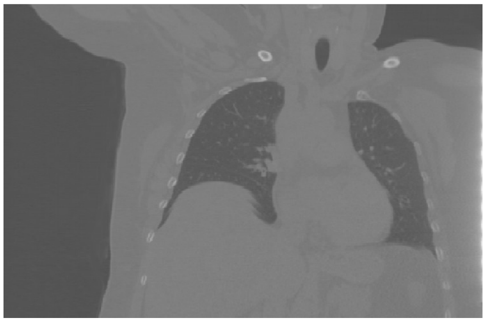


Figure 33: CT scan coronal plane, dummy not visible

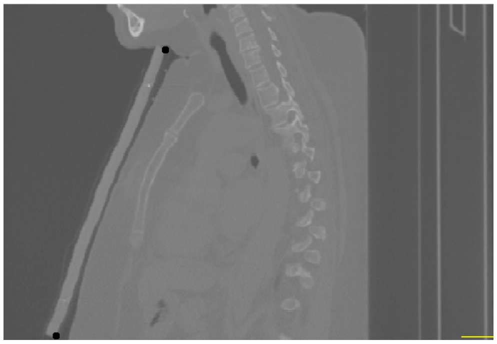


Figure 34: CT scan sagittal plane, outer points marked

The tool models the applicator on the position of Pa. Therefore, no additional translation of the modelled applicator is required. For the orientation, using basic goniometry, rotation angles can be determined with respect to Pa (figure 35 and 36).

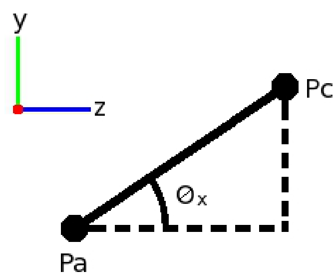


Figure 35: x-as rotation

$$\theta_x = \arctan\left(\frac{Pc_y - Pa_y}{Pc_z - Pa_z}\right)$$

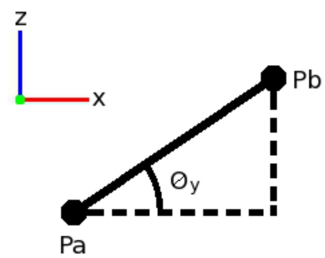


Figure 36: y-axis rotation

$$\theta_y = \arctan\left(\frac{Pb_z - Pa_z}{Pb_x - Pa_x}\right)$$

Unfortunately, due to asymmetry in applicator curvature, the location of Pb relative to Pa varies in y direction and therefore will not always be coplanar as can be seen in figure 30. Because of this, rotation around the z-axis needs to be determined differently. Therefore, the rotation between Pe and Pf are used.

After determining rotation, the modelled applicator has to be transformed with respect to the segmented patient anatomy. Because the applicator is highly sensitive to pixel errors, which could result in short circuit or other malfunctioning during simulation, the anatomy is transformed instead of the applicator. This way, the applicator can be modelled horizontally and will therefore not suffer to these flaws. Since rotation is determined with respect to Pa, the anatomy is rotated with respect to Pa.

After all transformations are done, the patient anatomy is ready for simulation. The tool will save the patient anatomy as a hierarchical data format file to be compatible with the other treatment planning tools. Figure 37 and 38 show a modelled applicator on a segmented patient anatomy. Here different indexes have different colours.

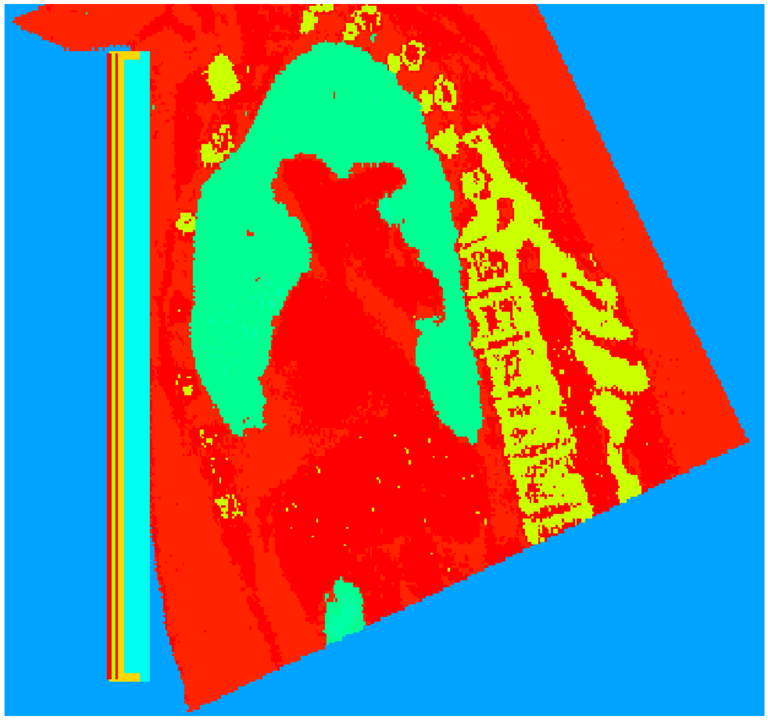


Figure 37 sagittal view

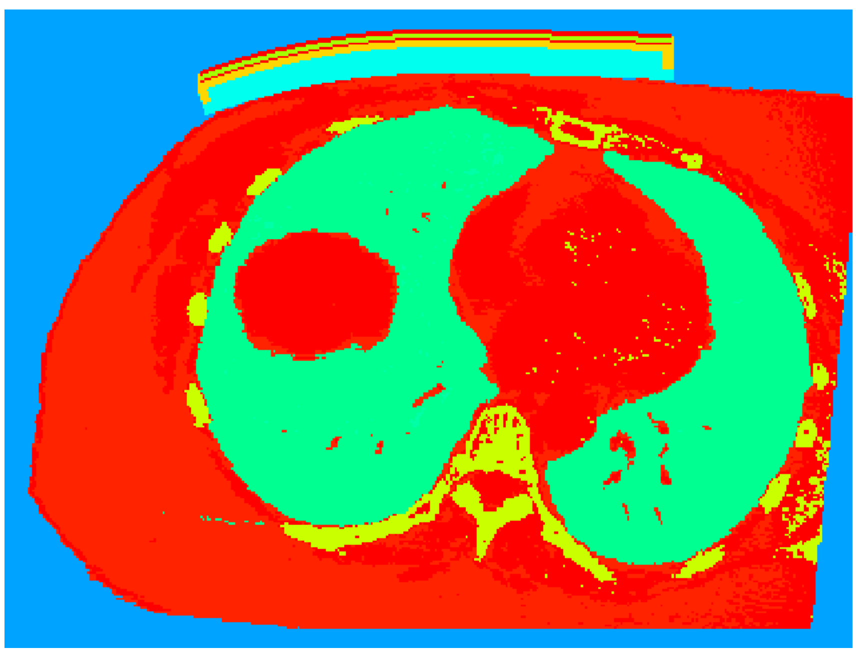


Figure 38: transverse view

5 Results

A software tool was developed that allows a user to model CFMA containing treatment specific characteristics. For this, treatment curvature for CFMA was studied. An appropriate way of estimating treatment curvature was investigated and the inter-variance of treatment curvature was analyzed. Throughout the different phases of the project, tests were done to confirm appropriate functioning.

In the **Requirements and Architecture** phase, detailed requirements were stated. In order to verify and validate the system, the software tool was tested for different curvatures and applicators in the Integration, test, and verification phase.

During **detailed design**, an approach to examine and model treatment curvature is developed. This curvature is verified on a real applicator with treatment curvature. Measurements on the inter-variance of real applicator curvature showed a mean maximum variance of 6 ±1.17 mm. This, compared to the modelled curvature displacement of maximal 1.98 ±0.99 mm, shows that the approach used for modelling CFMA is an adequate approach. Also, a technique to model the applicator was developed. This is tested by modeling different curvatures during implementation. Here, the software was tested and improved on CFMA with extreme curvature to ensure robustness.

In **Integration, Test, and Verification phase**, The software is tested on the user and system requirements. These requirements will now be reflected.

5.1. User requirements

The developed tool satisfies all stated user requirements. The requirements will be addressed priority based.

5.1.1 Must have

- **The user must be able to model bent applicators.**
  With the developed software tool in combination with a patient CT including a dummy antenna, a user is able to model bent CFMA.
- **The user must be able to define treatment position of the applicator.**
  The CFMA will be modelled based on coordinates defined in the parameter file. Using these coordinates, a user is able to define treatment position.
- **The user must be able to define treatment orientation of the applicator.**
  The CFMA will be modelled based on coordinates defined in the parameter file. Using these coordinates, a user is able to define treatment orientation.

5.1.2 Should have

- **System inputs via a parameter file.**
  Parameters can be provided using a parameter file.
- **Variable bolus thickness.**
  Water bolus thickness can be defined in the parameter file. It varies for different resolutions.
- **User labour input should take no longer than 5min.**
  Labour input is defined by extracting six coordinates out of the CT scan and declaring these coordinates, CT scan file, applicator type and bolus thickness in the parameter file. Depending on the skill of the operator, this should take around three minutes. This is less than the maximum of five minutes.
- **Execution time of the tool should take no longer than one day.**
  Current execution time takes about one minute. This is less than the maximum of one day.

5.1.3 Could have

- **The user could model multiple applicators on one patient anatomy.**
  Simulating multiple applicators will be done using superposition of the simulation per applicators. Therefore, modelling multiple applicators is not necessary.

5.2. System requirements

The software tool satisfies all must have and should have requirements. All system requirements will be addressed priority based.

5.2.1 Must have

- **The system must be able to model an applicator with rigid curvature.**
  All applicators can be modelled including treatment curvature.
- **The system must be able to model an applicator with treatment specific curvature.**
  All applicators can be modelled including treatment specific curvature.
- **All applicators are build up following the defined layer build up.**
  CFMA are build up following Kok et al. (2010).
- **The system must be able to model an applicator at a specified position relative to the patient anatomy.**
  CFMA's are modelled at the required treatment position.
- **The system must be able to model an applicator in the specified orientation relative to the patient anatomy.**
  CFMA's are modelled with treatment orientation implemented.

- **The modelled curvature displacement relative to the applicators curvature should be less than the inter-variance of the applicator curvature within a treatment.**
  The found mean maximum applicator treatment curvature inter-variance is about 6 ±1.17 mm (Appendix E, CFMA curvature inter-variance). The maximum found curvature displacement between modelling and treatment curvature is about 1.98 ±0.99 mm (Appendix D, Estimated applicator curvature measurements). Therefore, the system does satisfy to this requirement.
- **Software must be programmed in C++.**
  All software was written in C++.
- **The tool must be compatible with the current treatment planning system.**
  The output of the tool is a hierarchical data format file. This file can be read by the other tools and thus further treatment planning can be done.

5.2.2 Should have

- **The ability to have two bendings.**
  Because the left side of the curve is modelled separate from the right side, two different bendings can be modelled.
- **Variable bolus thickness.**
  The water bolus thickness can be adjusted using the parameter file and is therefore variable.
- **Automatically scaled bolus, rubber and substrate based on resolution.**
  The thickness of the water bolus, rubber frame and substrate is based on world sizes. Therefore the dimensions remain intact when the resolution is changed and thus this requirement is satisfied.

5.2.3 Could have

- **Torsion of the applicator included.**
  Torsion is not yet included in the software tool. However, the tool is developed in such a way that torsion of the applicators can easily be implemented.
- **Modelling multiple applicators on one segmented patient anatomy.**
  Simulation of multiple CFMA is done using superposition. Therefore it is not necessary to model more than one applicator at one patient file.

6 Conclusions and recommendations

Using the developed software tool, a user is able to successfully model treatment specific CFMA. Using a parameter file, the user can define the patient file, applicator type, water bolus thickness, applicator curvature, applicator position and applicator orientation. The tool satisfies all “must have” and “should have” requirements, fits within the treatment planning and is ready for further system verification and validation on patients. Although the software tool is complete, certain unsolved problems and possible vulnerabilities and improvements are encountered and have to be considered.

The dummy could be improved in two ways. At first, in order to make the user labour less time consuming and more accurate, small lead balls could be placed on the corners and centre of the dummy, as these are the points the user has to define at the CT scan. These lead balls will give a high contrast marker on the CT scan and are therefore more easy to see. Hereby, the user can locate these points faster and more accurate. For further improvement, the dummy's material consistence could be altered to better approximate the stiffness of the CFMA. Another improvement could be more treatment specific dummies for example through the use 3D printing dummies. These improvements will result in more representative curvature.

To counter the large treatment curvature inter-variance found, CFMAs should be fixed to a single curvature during the treatment period. This could for example be established by the use of 3D printed fixing parts. This could also be beneficial when applicator curvature is optimised, to enforce this optimum curvature on the different CFMA.

The defined resolution of the patient file, originating from the resolution of the CT scan, results in several distortions. During positioning of the CFMA, when transforming the patient, resolution is not changed. Although transforming is done using world coordinates, this may lead to unwanted situations. Also, due to the difference in resolution for the different x, y and z dimensions, distortion occurs when drawing layers with a single voxel thickness. Figure 39 and 40 show this distortion when drawing a curve in a coordinate system with a different x and y resolution, and later displayed in a coordinate system where the resolutions are the same.

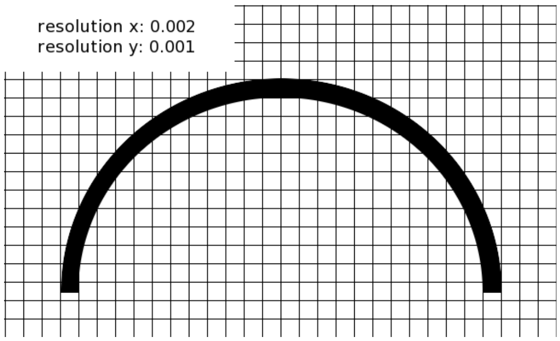


Figure 39: Curve drawn in non-equal resolution coordinate system

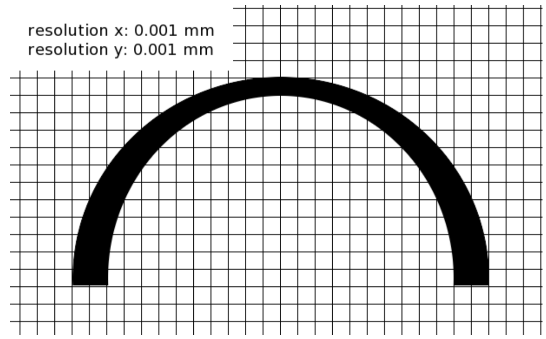


Figure 40: curve displayed in a equal resolution coordinate system

In the near future, it is advised to investigate the impact of the curvature inter-variance found within one patient. This can be done by simulating and comparing the different curvatures. Also, the improvements mentioned for the dummy antenna could possibly lead to significant improvement of curvature estimation. Furthermore, almost all treatment applicators show some sort of torsion. Torsion is currently not integrated in the software tool, while the effect of torsion is unknown. It is advised to expand the tool with torsion detection and modelling.

Epilogue

For me as a mechatronical student without a medical background, it was hard at first to adapt to the medical world. After reading several research papers about hyperthermia, I got familiar with the vocabulary and techniques, and learned a lot about radiotherapy. I had a great experience at the AMC.

Before starting this project, I set several personal goals for myself to develop. During this project, I achieved these goals. Beside these goals, I also wrote down my expectations. In this chapter, my goals and expectations are reflected.

My personal goals and expectations were:

- **Get acquainted with the biomedical side of Mechatronics;**
  I have experienced mechatronical applications in the hospital. I attended superficial hyperthermia treatments and read several research papers. Furthermore, every Tuesday I attended radiotherapy meetings and radiotherapy research meetings. Here, new methods, research results and problems are presented and discussed. Here, for example, I learned about delineation of tumours, proton and photon therapy and 4D MRI.
- **Determine whether I want to do a master in Biomedical engineering;**
  Thanks to the experience I gained from the radiotherapy meetings and radiotherapy research meetings, I have a better understanding of what biomedical engineering comprehends. At the radiotherapy department at the AMC, it can be developing or improving medical devices such as the MRI, linear accelerator or CFMA. It also includes developing new methods and techniques for treatment planning and all research related to this. I was able to determine whether I want to do a biomedical engineering master.
- **Get a better understanding of labour and interpersonal relations within a big organisation;**
  My previous traineeships were in a small organisations. I have experienced the differences between smaller and bigger organisation. For instance, coaching is better coordinated and there are more opportunities to develop yourself within a bigger organisation. However, the interaction is less personal for a bigger organisation.
- **Get a better understanding of labour and interpersonal relations within a research organisation;**
  I have attended several radiotherapy research meetings. Here, researchers discuss their results or problems thoroughly. The atmosphere is friendly and informal. The workload does not seem too high and a certain amount of freedom to do the research is given.

- **Determine whether I want to go into research;**
  I like the critical eye and the way of thinking. Although it has enough challenge, it may be too focused on a single topic for me.
- **More experience in modelling/simulating;**
  I gained considerable more knowledge of modelling. During programming, I learned new approaches to model objects. I learned about different simulation techniques, and its difficulties. Furthermore, I read research about the development of the deep hyperthermia treatment planning system. For example, the finite difference time domain (FDTD) method, based on the Maxwell's equations used to simulated E-field distributions in different types of tissue. And the temperature distribution.
- **Gaining considerable experience in C++ programming.**
  All software is written in C++. For some elements, using/adapting the existing software was required. I hereby encountered different techniques and had make them my own.

My expectations were:

- **I will see biomedical implementation(s) of Mechatronics;**
  Within the radiotherapy alone, mechatronics implementations are not used as much as it could be. There is plenty of room for improvement and automation, which could be achieved with mechatronical devices. For example the placing and bending of the CFMA on the patient. This is currently done by hand. This introduces many human errors. A robot arm in combination with vision technique could replace applicator placing and holding, and therewith reducing human errors.
- **I learn how hyperthermia works and is applied;**
  I attended superficial hyperthermia treatments and read several research papers about hyperthermia, resulting in a basic knowledge of hyperthermia. Although there is a clear protocol for the application of hyperthermia, physicians act differently on certain situations and interpretation of the protocol divers.
- **At the end of my project, superficial hyperthermia treatment planning is complete and ready to be tested.**
  The tool set of superficial hyperthermia treatment planning is now complete. The system is ready for simulation of bent CFMA on patient anatomy.

Bibliography

AMC @ a glance - Academisch Medisch Centrum. (n.d.). Retrieved February 19, 2016, from https://www.amc.nl/web/research/researchamc/amc-a-glance.htm

Bruijne, M. D. E., Zee, J. V. A. N. D. E. R., Ameziane, A. L. I., & Rhoon, G. C. V. A. N. (2011). *Quality control of superficial hyperthermia by treatment evaluation* (Vol. 27). http://doi.org/10.3109/02656736.2010.525226

Cihoric, N., Tsikkinis, A., van Rhoon, G., Crezee, H., Aebersold, D. M., Bodis, S., … Ghadjar, P. (2015). Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *00*(00), 1–6. http://doi.org/10.3109/02656736.2015.1040471

Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M., & Engelstein, D. (2011). Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU International*, *107*(6), 912–918. http://doi.org/10.1111/j.1464-410X.2010.09654.x

Griffin, R. J., Dings, R. P. M., Jamshidi-Parsian, A., & Song, C. W. (2010). Mild temperature hyperthermia and radiation therapy: role of tumor vascular thermotolerance and relevant physiological factors. *July*, 256–263. http://doi.org/10.1016/j.surg.2006.10.010.Use

Gvs14. (2012). planes. Retrieved May 17, 2016, from https://anatomystudybuddy.wordpress.com/2012/09/19/sagittal-transverse-and-coronal-planes/

Issels, R. D., Lindner, L. H., Verweij, J., Wust, P., Reichardt, P., Schem, B. C., … Hohenberger, P. (2010). Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: A randomised phase 3 multicentre study. *The Lancet Oncology*, *11*(6), 561–570. http://doi.org/10.1016/S1470-2045(10)70071-1

Jones, E. L., Oleson, J. R., Prosnitz, L. R., Samulski, T. V., Vujaskovic, Z., Yu, D., … Dewhirst, M. W. (2005). Randomized trial of hyperthermia and radiation for superficial tumors. *Journal of Clinical Oncology*, *23*(13), 3079–3085. http://doi.org/10.1200/JCO.2005.05.520

Kampinga, H. H. (2006). Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *22*(3), 191–196. http://doi.org/10.1080/02656730500532028

Kok, H. P., Correia, D., Greef, M. De, Stam, G. Van, Bel, A., Crezee, J., … Crezee, J. (2010). SAR deposition by curved CFMA-434 applicators for superficial hyperthermia : Measurements and simulations, (February), 171–184. http://doi.org/10.3109/02656730903397321

Kok, H. P., De Greef, M., Correia, D., Vörding, P. J. Z. V. S., Van Stam, G., Gelvich, E. a, … Crezee, J. (2009). FDTD simulations to assess the performance of CFMA-434 applicators for superficial hyperthermia. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *25*(6), 462–476. http://doi.org/10.1080/02656730903008493

Overgaard, J., Gonzalez Gonzalez, D., Hulshof, M. C., Arcangeli, G., Dahl, O., Mella, O., & Bentzen, S. M. (1995). Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. *Lancet*, *345*(8949), 540–543. http://doi.org/10.1016/S0140-6736(95)90463-8

van der Zee, J. (2002). Heating the patient: A promising approach? *Annals of Oncology*, *13*(8), 1173–1184. http://doi.org/10.1093/annonc/mdf280

van der Zee, J., González González, D., van Rhoon, G. C., van Dijk, J. D., van Putten, W. L., & Hart, A. A. (2000). Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet*, *355*(9210), 1119–1125. http://doi.org/10.1016/S0140-6736(00)02059-6

Vernon, C. C., Hand, J. W., Field, S. B., Machin, D., & Whaley, J. B. (1996). Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int. J. Radiation Oncology Biol.Phys.*, *35*(4), 731–744. http://doi.org/10.1016/0360-3016(96)00154-X

V-model - Wikipedia. (n.d.). Retrieved May 2, 2016, from https://nl.wikipedia.org/wiki/V-model

Westra, A., & Dewey, W. (1971). Variation in sensitivity to heat shock during the cell-cycle of Chinese hamster cells in vitro. *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine*, *19*, 467–477.

Appendix

A) Plan of Approach;

B) Applicator curvature measurements;

C) CFMA treatment curvature inter-variance;

D) Activity Diagram;

E) Internal Block Diagram applicator modelling tool;

F) Use Case Diagram.

Appendix A) Plan of Approach

Table of Contents

Background

This Plan of Approach is being written in the case of a graduation project conducted by Jort Groen, student Mechatronics at The Hague University of Applied Sciences, The Netherlands.

This project was commissioned by the Academic Medical Center, University of Amsterdam, The Netherlands.

“The Academic Medical Center (AMC) is one of the foremost research institutions in the Netherlands, as well as one of its largest hospitals. Over 7000 people work here to provide integrated patient care, fundamental and clinical scientific research, and teaching.” (“AMC @ a glance - Academisch Medisch Centrum,”)

The AMC is one of the few institutes where clinical application of hyperthermia is applied. Here, both superficial and deep hyperthermia treatments are given as part of a combined modality against cancer. Currently, planning for superficial hyperthermia treatment is in development. There is plenty of room for improvement of medical care.

This document has the following purposes:

- Giving a short introduction to superficial hyperthermia treatment;
- Describing the purpose of the project;
- Describing the problem;
- Specifying the deliverables and project activities throughout the project;
- Describing the boundaries of the project;
- Giving an estimated planning of the course of the project.

Throughout the next chapters, these topics will thoroughly be addressed.

1. Introduction

Treatment of malignant tumours includes several techniques. In some cases, surgery alone is sufficient. When surgery cannot be applied or as part of a multidisciplinary approach, radio and/or chemotherapy are used. In this last case, radio and/or chemotherapy can be applied either prior to, or after surgery.

A less widely known treatment modality is hyperthermia. Hyperthermia, i.e. heating tumour temperature in the range of 40-45°C, is a very effective radiation- and chemosensitizer. Over twenty randomized clinical trials showed significant improvement in clinical outcome from hyperthermia in combined treatment with radiation and/or chemotherapy (Kampinga, 2006), (Cihoric et al., 2015). Hyperthermia has proven effective, e.g. malignant melanoma (Overgaard et al., 1995), bladder cancer (Colombo et al., 2011), cervical cancer (van der Zee et al., 2000), soft tissue sarcoma (Issels et al., 2010) and recurrent breast cancer (Vernon, Hand, Field, Machin, & Whaley, 1996).

At the AMC, Contact Flexible Microstrip Applicators (CFMA) are applied for superficial hyperthermia. A CFMA consists of an antenna, operating at 434 MHz, and a water bolus. A CFMA during treatment is shown in figure 1. The water bolus, located between the antenna and the skin, directs the electromagnetic field from the antenna to the tissue and can also be used to heat or cool the skin. The antenna is used for heating tissue, up to ~4cm deep. The CFMA is available in five different sizes and can be bent in the direction perpendicular to that of the field. The water bolus varies in thickness per treatment. The deformation and size of the antenna, and the thickness of the bolus affects the electromagnetic field distribution of an applicator.

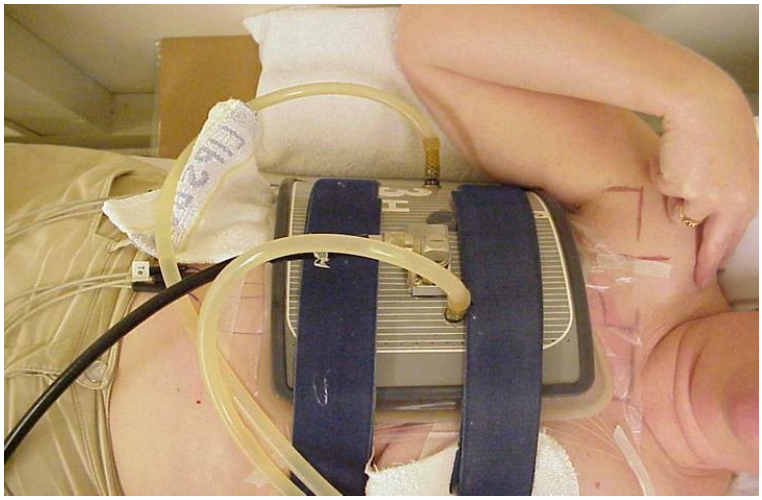


Figure 1: Superficial hyperthermia treatment on recurrent breast cancer

During hyperthermia treatments, thermometry is limited due to a limited number of sensors that incompletely measure the target volume. For example, patients have around forty measure points at the skin surface and seven inside the target area. This shows the heat distribution on the skin surface, but does not give an adequate 3D representation. A way to obtain more insight in the achieved temperatures in the heated tissue is by simulating the treatment during hyperthermia treatment planning. (Kok et al., 2009) The AMC currently utilizes a treatment planning system only for deep hyperthermia.

The hyperthermia planning system consists of an assortment of software tools. Different tools are used for different tasks depending on the situation. The planning is done in several steps:

At first, the patient anatomy is modelled. For this, a CT scan is made. On this scan, segmentation of tissue types e.g. bone, fat, muscle, etc. is done. Secondly, the applicators are modelled at the segmented patient anatomy. After this, the electromagnetic field power distribution is calculated (Specific Absorption Rate, SAR ($W\ kg^{-1}$)). Finally, using the SAR distribution, temperature distribution is calculated and visualized with a 3D representation. With the 3D representation of the temperatures inside the patient anatomy, treatment can be optimized.

2. Purpose of the project

With this project, the AMC would like to accomplish the following:

Improve clinical outcome of malignant tumour treatment with superficial hyperthermia treatment planning.

In general, simulations of a treatment can help to optimise the treatment strategy. This is because of the predictive capability of simulations. The clinical relevance of hyperthermia treatment planning is also emphasized in the Quality Assurance Guidelines for clinical application of loco regional hyperthermia (Bruggmoser et al., 2012); (Myerson et al., 2014). In addition, hyperthermia treatment planning can be a valuable tool in the evaluation of steering actions and what-if scenarios. (de Bruijne, Ameziane, & van Rhoon, 2011)

3. The problem

For the planning of superficial hyperthermia treatments, most of the software developed for deep hyperthermia can be used. As an addition, in order to reproduce the treatment position and orientation of an applicator relative to the body anatomy, a dummy antenna is placed on the patient during the CT scan. This dummy antenna is placed at the desired treatment pose with the treatment curvature implemented.

Using the existing planning tools, a straight antenna can be modelled and simulated (Figure 2). However during treatments, applicators are most commonly bent because of curvature of the patient's body. The current planning system for hyperthermia treatment lacks the ability to correctly model bent CFMA. Therefore, reliable simulations cannot be made and treatment planning cannot be applied. Additional software is required to model treatment-specific curved applicators.

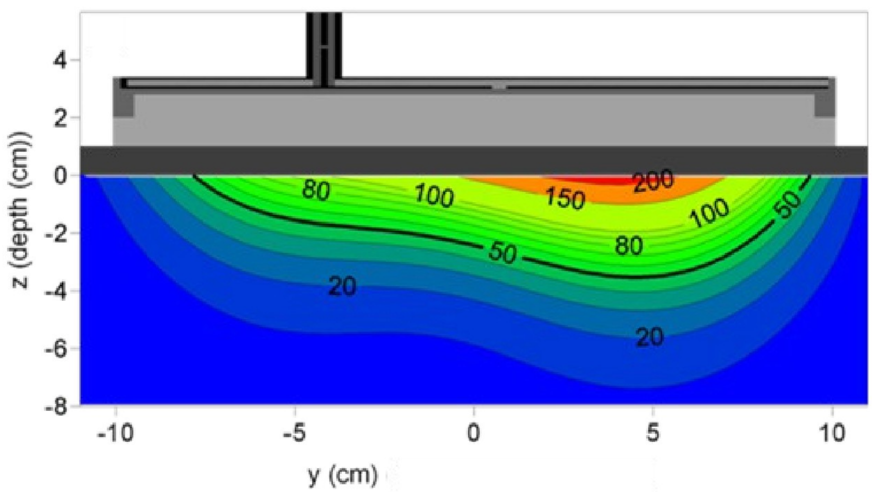


Figure 2: SAR distribution (W/kg) for a straight antenna

4. Project results

The goal of this project is: Complementing superficial hyperthermia treatment planning.

In order to complement the planning system, additional software is required. After complementing, the planning system can be applied for clinical use.

4.1. Deliverables

To make superficial hyperthermia treatment planning suitable for clinical use, the following products will be delivered for the end of the project:

- **A tool for modelling bent CFMA.**

A software tool to model treatment-specifically bent applicators at the segmented patient anatomy. This has to be done considering the CFMA type, position, orientation and curvature.

- **A tool for determining curvature.**

A software tool to determine treatment applicator curvature, extracted from a CT scan containing an applicator dummy.

5. Project activities

Several activities will be carried out during the project to create the deliverables:

1. **Starting up**
   - **1.1.** Background reading
   - **1.2.** Setting up Plan of Approach
2. **Automatic modelling of bent CFMA**
   - **2.1.** Studying existing software
   - **2.2.** Finding possibilities
   - **2.3.** Evaluating possibilities
   - **2.4.** Developing software
3. **Curvature recognition**
   - **3.1.** Getting familiar with the existing software
   - **3.2.** Finding possibilities
   - **3.3.** Evaluating possibilities
   - **3.4.** Developing software
4. **Finalizing project**
   - **4.1.** Testing and finalizing software
   - **4.2.** Finalizing rapport

5.1. Starting up

5.1.1. Background reading

Research is studied to get more knowledge about the physical, biological and clinical aspects of hyperthermia. This is done to get a clear understanding of what the project comprehends, and what can be expected.

5.1.2. Setting up Plan of Approach

A Plan of Approach is written, describing the problem and clarifying the scope of the project.

5.2. Automatic modelling of bent CFMA

5.2.1. Studying existing software

The existing software for modelling straight applicators is studied. This will give a better understanding of how to compose curved applicators in the simulation.

5.2.2. Finding possibilities

There different ways/approaches are investigated for correctly modelling bent applicators.

5.2.3. Evaluating possibilities

A strategy is developed using the found possibilities. This includes trying different methods.

5.2.4. Developing software

Using the developed strategy, a software tool is developed to properly model bent applicators.

5.3. Curvature recognition

5.3.1. Getting familiar with the existing software

The existing software for the deep hyperthermia treatment planning is being examined to get a better understanding of the general build-up and the possibilities for making curvature recognition.

5.3.2. Finding possibilities

There will be searched for different ways/approaches to make curvature recognition possible.

5.3.3. Evaluating possibilities

The found possibilities are compared, and a solution is chosen.

5.3.4. Developing software

The chosen solution is elaborated, the curvature recognition is written.

5.4. Finalizing project

5.4.1. Testing and finalizing software

The tools are tested and bettered until it complies with all the requirements.

5.4.2. Finalizing rapport

All the documentation of the separate activities are combined and put into one end rapport.

6. Project boundaries

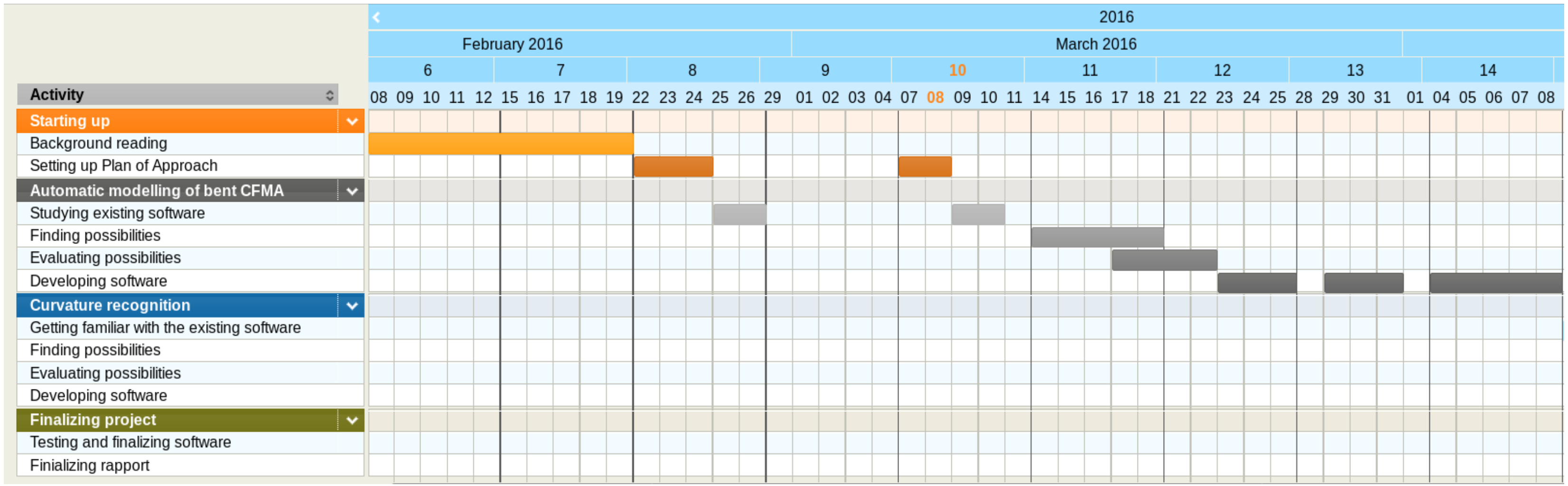
This project is planned from Monday, February 8th up to June 2016.
A weekly meeting with the project mentors is planned at Tuesday 10:00 am.

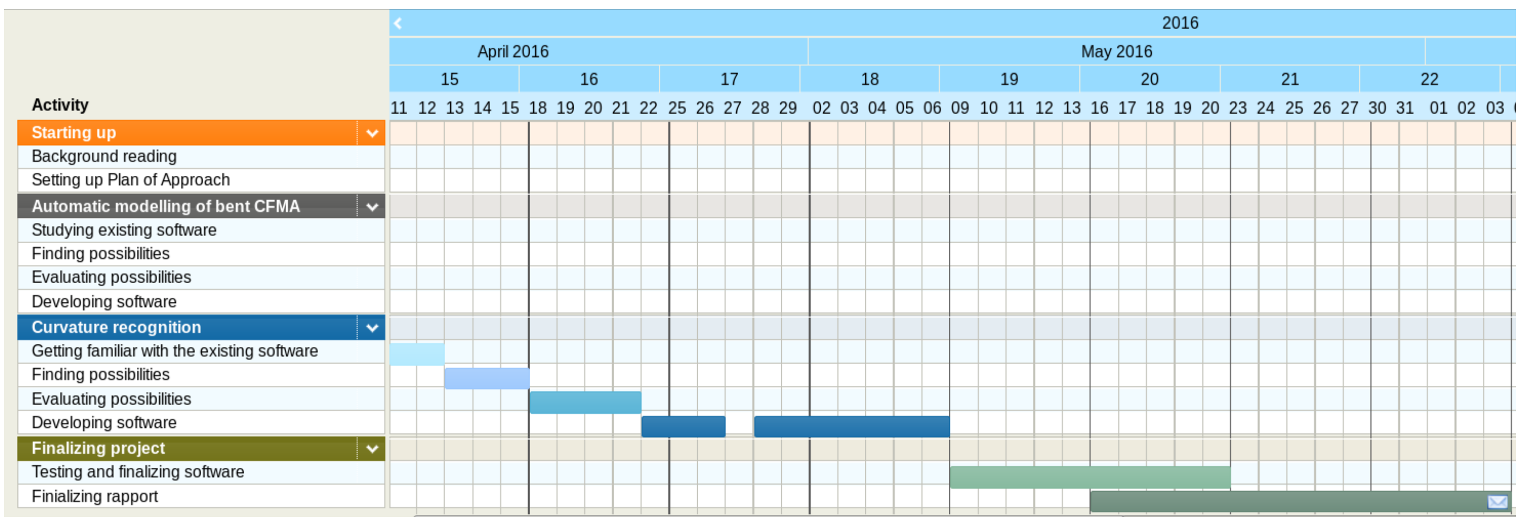
Boundaries

- Software will mainly be written in C++;
- Bending is only done around the axis perpendicular to the field direction;
- For all applicators, a simplified yet representative model will be created;
- Position, orientation, applicator type and bolus thickness will be manual input for the system;
- For the 1H applicator, the “inductance boxes” will not be modelled.

A CT scan of a patient with an applicator dummy will be provided by the AMC.
Source code of the existing planning system will also be provided by the AMC.

7. Planning


2016
February 2016
March 2016
6 7 8 9 10 11 12 13 14
08 09 10 11 12 15 16 17 18 19 22 23 24 25 26 29 01 02 03 04 07 08 09 10 11 14 15 16 17 18 21 22 23 24 25 28 29 30 31 01 04 05 06 07 08
Activity
Starting up
Background reading
Setting up Plan of Approach
Automatic modelling of bent CFMA
Studying existing software
Finding possibilities
Evaluating possibilities
Developing software
Curvature recognition
Getting familiar with the existing software
Finding possibilities
Evaluating possibilities
Developing software
Finalizing project
Testing and finalizing software
Finializing rapport


2016
April 2016
May 2016
15 16 17 18 19 20 21 22
11 12 13 14 15 18 19 20 21 22 25 26 27 28 29 02 03 04 05 06 09 10 11 12 13 16 17 18 19 20 23 24 25 26 27 30 31 01 02 03
Activity
Starting up
Background reading
Setting up Plan of Approach
Automatic modelling of bent CFMA
Studying existing software
Finding possibilities
Evaluating possibilities
Developing software
Curvature recognition
Getting familiar with the existing software
Finding possibilities
Evaluating possibilities
Developing software
Finalizing project
Testing and finalizing software
Finializing rapport

8. Personal goals

My personal goals are:

- Get acquainted with the biomedical side of Mechatronics;
- Determine whether I want to do a master in Biomedical Engineering;
- Get a better understanding of labour and interpersonal relations within a big organisation;
- Get a better understanding of labour and interpersonal relations within a research organisation;
- Determine whether I want to go into research;
- More experience in modelling/simulating;
- Gaining considerable experience in C++ programming.

My expectations are:

- I will see biomedical implementation(s) of Mechatronics;
- I get to know how people work together in a bigger organisation, in this case a hospital;
- I see how it is to be in research;
- I learn about radiotherapy;
- I learn how hyperthermia works and is applied;
- I get more experience with modelling and simulating;
- I gain considerable more skills in programming in C++;
- At the end of my project, superficial hyperthermia treatment planning is complete and ready to be tested.

Bibliography

AMC @ a glance - Academisch Medisch Centrum. (n.d.). Retrieved February 19, 2016, from https://www.amc.nl/web/research/researchamc/amc-a-glance.htm

Bruggmoser, G., Bauchowitz, S., Canters, R., Crezee, H., Ehmann, M., Gellermann, J., … Van Rhoon, G. (2012). Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia. *Strahlentherapie Und Onkologie*, *188*(SUPPL. 2), 198–211. http://doi.org/10.1007/s00066-012-0176-2

Cihoric, N., Tsikkinis, A., van Rhoon, G., Crezee, H., Aebersold, D. M., Bodis, S., … Ghadjar, P. (2015). Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *00*(00), 1–6. http://doi.org/10.3109/02656736.2015.1040471

Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M., & Engelstein, D. (2011). Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU International*, *107*(6), 912–918. http://doi.org/10.1111/j.1464-410X.2010.09654.x

de Bruijne, M., Ameziane, A., & van Rhoon, G. C. (2011). *Quality control of superficial hyperthermia by treatment evaluation*.

Issels, R. D., Lindner, L. H., Verweij, J., Wust, P., Reichardt, P., Schem, B. C., … Hohenberger, P. (2010). Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: A randomised phase 3 multicentre study. *The Lancet Oncology*, *11*(6), 561–570. http://doi.org/10.1016/S1470-2045(10)70071-1

Kampinga, H. H. (2006). Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *22*(3), 191–196. http://doi.org/10.1080/02656730500532028

Kok, H. P., De Greef, M., Correia, D., Vörding, P. J. Z. V. S., Van Stam, G., Gelvich, E. a, … Crezee, J. (2009). FDTD simulations to assess the performance of CFMA-434 applicators for superficial hyperthermia. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *25*(6), 462–476. http://doi.org/10.1080/02656730903008493

Myerson, R. J., Moros, E. G., Diederich, C. J., Haemmerich, D., Hurwitz, M. D., Hsu, I.-C. J., … Stauffer, P. R. (2014). Components of a hyperthermia clinic: recommendations for staffing, equipment, and treatment monitoring. *International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *30*(1), 1–5. http://doi.org/10.3109/02656736.2013.861520

Overgaard, J., Gonzalez Gonzalez, D., Hulshof, M. C., Arcangeli, G., Dahl, O., Mella, O., & Bentzen, S. M. (1995). Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. *Lancet*, *345*(8949), 540–543. http://doi.org/10.1016/S0140-6736(95)90463-8

van der Zee, J., González González, D., van Rhoon, G. C., van Dijk, J. D., van Putten, W. L., & Hart, A. A. (2000). Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet*, *355*(9210), 1119–1125. http://doi.org/10.1016/S0140-6736(00)02059-6

Vernon, C. C., Hand, J. W., Field, S. B., Machin, D., & Whaley, J. B. (1996). Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int. J. Radiation Oncology Biol.Phys.*, *35*(4), 731–744. http://doi.org/10.1016/0360-3016(96)00154-X

Appendix B) User requirements

User requirements

Must have

- The user must be able to model bent applicators.
- The user must be able to define treatment position of the applicator.
- The user must be able to define treatment orientation of the applicator.

Should have

- System inputs via a parameter file.
- Variable bolus thickness.
- User labour input should take no longer than 5min.
- Execution time of the tool should take no longer than one day.

Could have

- The user could model multiple applicators on one patient anatomy.

Won't have

- Automatic applicator detection.
- Automatic position detection.

Appendix C) System requirements

System requirements

Must have

- The system must be able to model an applicator with rigid curvature.
- The system must be able to model an applicator with treatment specific curvature.
- All applicators are build up following the defined layer build up.
- The system must be able to model an applicator at a specified position relative to the patient anatomy.
- The system must be able to model an applicator in the specified orientation relative to the patient anatomy.
- The modelled curvature displacement relative to the applicators curvature should be less than the inter-variance of the applicator curvature within a treatment.
- Software must be programmed in C++.
- The tool must be compatible with the current treatment planning system.

Should have

- The ability to have two bendings
- Variable bolus thickness.
- Automatically scaled bolus, rubber and substrate based on resolution.

Could have

- Torsion of the applicator included.
- Modelling multiple applicators on one segmented patient anatomy.

Won't have

- Curvature along the electromagnetic field lines.
- The ability to have more than two deformations.

Appendix D) Estimated applicator curvature measurements

Applicator curvature measurements

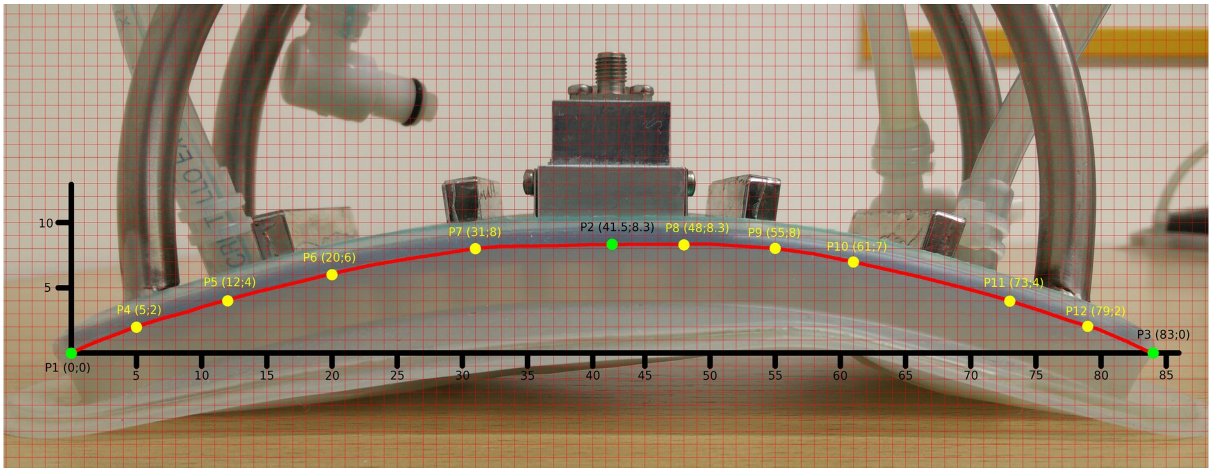
Purpose: The objective of this test was to measure the difference between a real applicator curvature and an estimated modelled curvature consisting out of two separate second-degree polynomial functions.

Methods and Materials: Photographs are taken and horizontal lengths of the applicators are measured of all different CFMA, each including treatment curvature. The photographs are all taken from the same position and angle relative to the applicator. Each photograph is overlaid with a grid and the three points P1, P2 and P3 are drawn. Then, a line is drawn following the treatment curvature. On this line, additional points are drawn P4 - P12. Using points P1, P2 and P3, (based on the grid location) the two polynomial functions are composed (left side and right side). Using these functions, the additional points (P4 - P12) are verified and the differences are noted. Thereafter, differences, minimum differences, maximum differences and mean differences are calculated. All results are also converted to millimetre using the horizontal measured length.

The following inaccuracies are not taken into account: Angle and position variance of the camera, rotation and centre offset of the applicator, camera lens distortions, grid placement inaccuracy, function composition inaccuracy and horizontal length measurement inaccuracy.

Results: The maximum inaccuracy measured is an offset of 1.98 ±0.99 mm.

A 1H02110

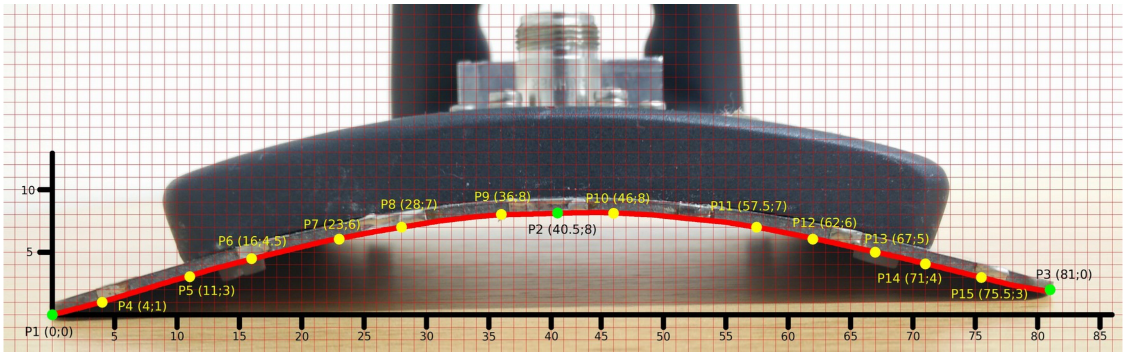


Formula left: $-0.00481928x^2 + 0.4x + 0$
Formula right: $-0.00481928x^2 + 0.4x + 0$

scale: 1/ 2.36
tolerance: ±0.708

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	41.5;8.3	8.3	0	0
P3	83;0	0	0	0
P4	5;2	1.88	0.12	0.28
P5	12;4	4.11	0.11	0.26
P6	20;6	6.07	0.07	0.17
P7	31;8	7.77	0.23	0.54
P8	48;8.3	8.10	0.1	0.24
P9	55;8	7.42	0.58	1.37
P10	61;7	6.47	0.53	1.25
P11	73;4	3.52	0.48	1.13
P12	79;2	1.52	0.48	1.13
min			0.07	0.17
max			0.58	1.37
avrg			0.3	0.71

A 2H02110



Formula left $f(x) = -0.00487731x^2 + 0.395062x + 0$

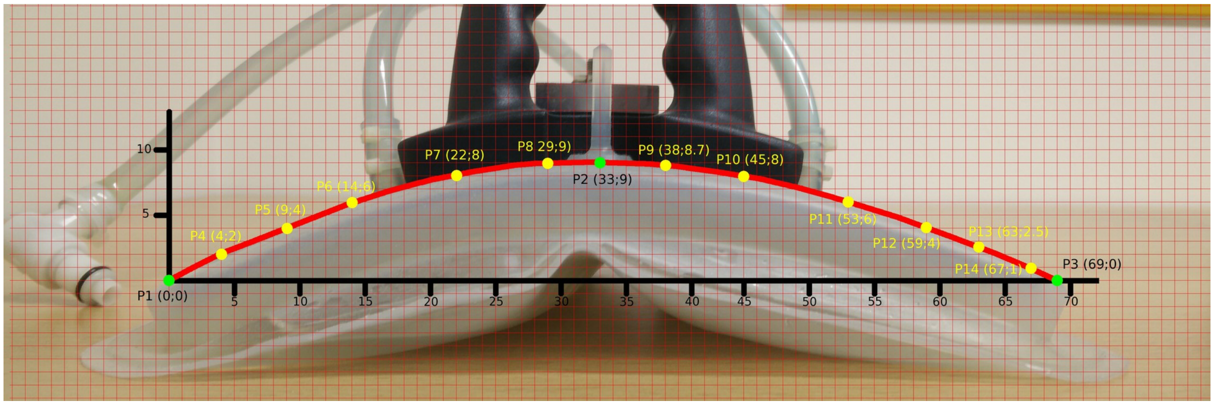
Formula right $f(x) = -0.00487731x^2 + 0.395062x + 0$

Scale: 1/1.75

Tolerance: 0.53mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	40.5;8	8	0	0
P3	81;0	0	0	0
P4	4;1	1.5	0.5	0.88
P5	11;3	3.76	0.76	1.33
P6	16;4.5	5.07	0.57	1.00
P7	23;6	6.51	0.51	0.89
P8	28;7	7.24	0.24	0.42
P9	36;8	7.90	0.1	0.18
P10	46;8	7.85	0.15	0.26
P11	57.5;7	6.59	0.41	0.72
P12	62;6	5.75	0.25	0.44
P13	67;5	4.57	0.43	0.75
P14	71;4	3.46	0.54	0.95
P15	75.5;3	2.03	0.97	1.70
min			0.1	0.18
max			0.97	1.70
avrg			0.45	0.79

A 4H02110

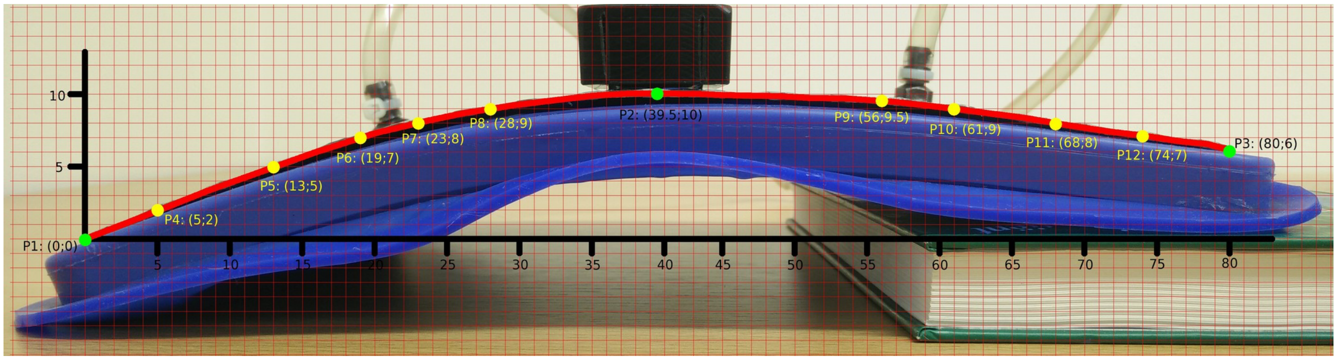


Formula left: f(x)= $-0.00826446x^2 + 0.545455x + 0$
Formula right: f(x)= $-0.00694444x^2 + 0.458333x + 1.4375$

Scale: 1/ 2.64
Tolerance: ±0.79mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	33;9	9	0	0
P3	69;0	0	0	0
P4	4;2	2.05	0.05	0.32
P5	9;4	4.23	0.77	2.03
P6	14;6	6.02	0.02	0.05
P7	22;8	8.00	0	0
P8	29;9	8.87	0.13	0.34
P9	38;8.7	8.79	0.09	0.24
P10	45;8	8.00	0.00	0
P11	53;6	6.22	0.22	0.58
P12	59;4	4.31	0.31	0.82
P13	63;2.5	2.75	0.25	0.66
P14	67.1	0.92	0.08	0.21
min			0	0
max			0.77	2.03
avrg			0.17	0.48

5H04108

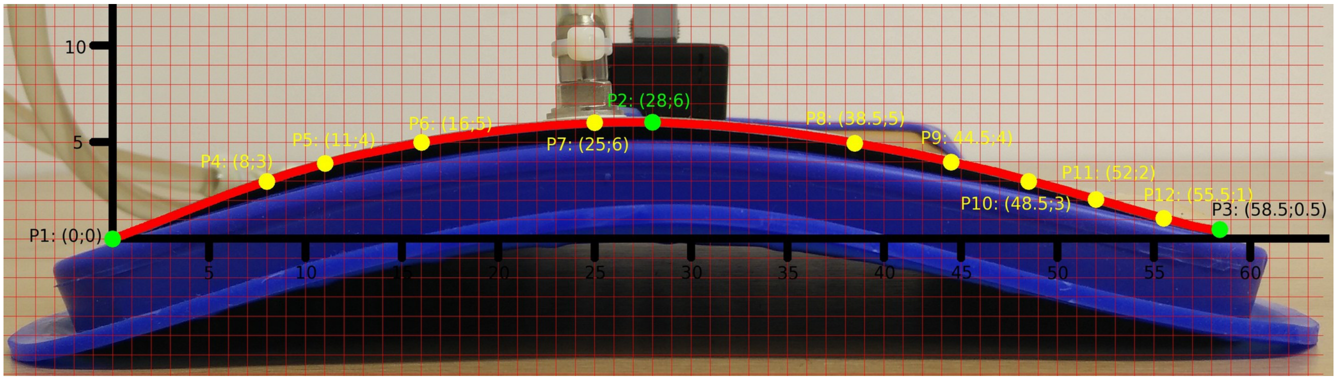


Formula left: $f(x) = -0.00826446x^2 + 0.545455x + 0$
Formula right: $f(x) = -0.00694444x^2 + 0.458333x + 1.4375$

Scale: 1/3.44
Tolerance: ±1mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	39.5;10	10	0	0
P3	80;6	6	0	0
P4	5;2	2.37	0.17	0.58
P5	13;5	5.50	0.5	1.72
P6	19;7	7.31	0.31	1.07
P7	23;8	8.26	0.26	0.89
P8	28;9	9.15	0.15	0.52
P9	56;9.5	9.34	0.16	0.55
P10	61;9	8.88	0.12	0.41
P11	68;8	8.02	0.02	0.07
P12	74;7	7.10	0.10	0.34
min			0.02	0.07
max			0.5	1.72
avrg			0.2	0.68

3H081110

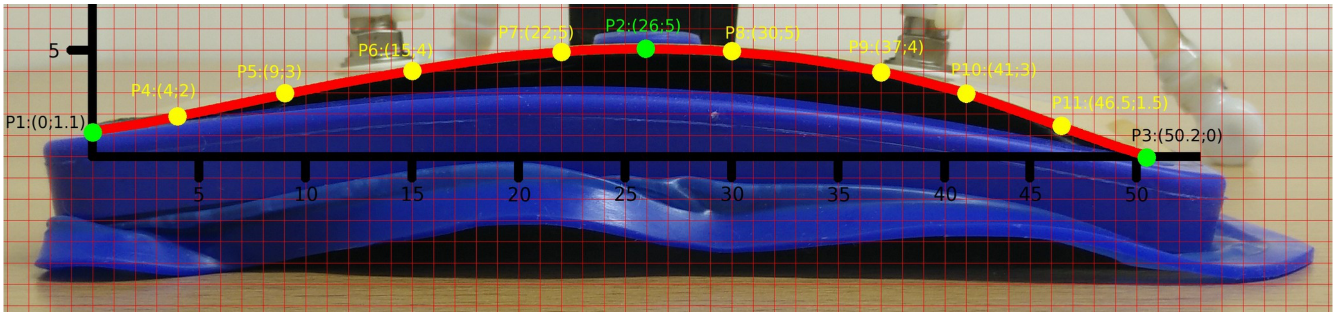


Formula left: $f(x) = -0.00765306x^2 + 0.428571x + 0$
Formula right: $f(x) = -0.00591239x^2 + 0.331094x + 1.36469$

Scale: 1/3.3
Tolerance: ± 0.99 mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	28;6	6	0	0
P3	58.5;0.5	0.5	0	0
P4	8;3	2.94	0.06	0.20
P5	11;4	3.79	0.21	0.69
P6	16;5	4.90	0.1	0.33
P7	25;6	5.93	0.07	0.23
P8	38.5;5	5.35	0.15	0.49
P9	44.5;4	4.39	0.39	1.3
P10	48.5;3	3.52	0.52	1.71
P11	52;2	2.60	0.60	1.98
P12	55.5;1	1.53	0.53	1.75
min			0.06	0.2
max			0.60	1.98
avrg			0.29	0.96

4H051110

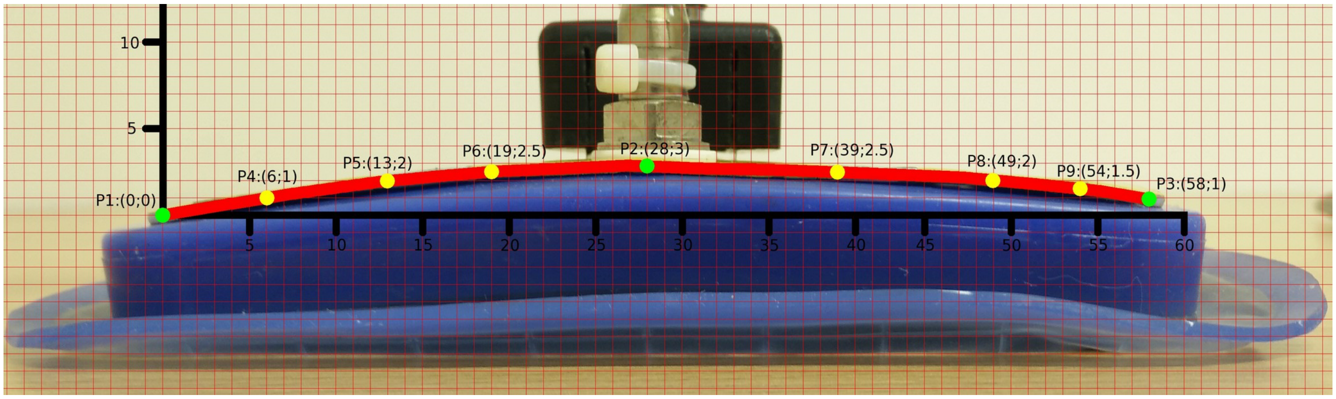


Formula left: $f(x) = -0.00576923x^2 + 0.3x + 1.1$
Formula right: $f(x) = -0.00853767x^2 + 0.443959x + -0.771464$

Scale: 1/3.66
Tolerance: ±1.1 mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;1.1	1.1	0	0
P2	26;5	5	0	0
P3	50.2;0	0.08	0.08	0.29
P4	4;2	2.21	0.21	0.77
P5	9;3	3.33	0.33	1.21
P6	15;4	4.3	0.3	1.1
P7	22;5	4.9	0.1	0.37
P8	30;5	4.86	0.14	0.51
P9	37;4	3.97	0.03	0.11
P10	41;3	3.08	0.08	0.29
P11	46.5;1.5	1.41	0.09	0.33
min			0.03	0.11
max			0.33	1.21
avrg			0.16	0.59

2H031101

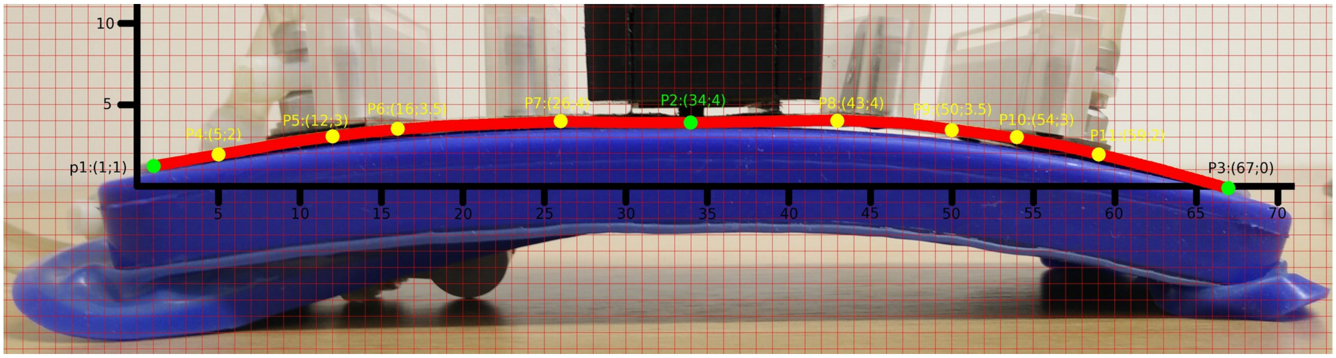


Formula left: $f(x) = -0.00382653x^2 + 0.214286x + 0$
Formula right: $f(x) = -0.00222222x^2 + 0.124444x + 1.25778$

Scale: 1/2.39
tolerance: ± 0.72mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	0;0	0	0	0
P2	28;3	3	0	0
P3	58;1	1	0	0
P4	6;1	1.15	0.15	0.36
P5	13;2	2.14	0.14	0.33
P6	19;2.5	2.69	0.19	0.45
P7	39;2.5	2.7	0.2	0.48
P8	49;2	2.02	0.02	0.05
P9	54;1.5	1.5	0	0
min			0	0
max			0.2	0.48
avrg			0.12	0.28

1H011101



Formula left: $f(x) = -0.00275482x^2 + 0.187328x + 0.815427$
Formula right: $f(x) = -0.00367309x^2 + 0.24977x + -0.246097$

Scale: 1/2.76
Tolerance: ±0.83 mm

Point	Location on grid	Calculated location	Offset in s	Real offset in mm
P1	1;1	1	0	0
P2	34;4	4	0	0
P3	67;0	0	0	0
P4	5;2	1.68	0.32	1.02
P5	12;3	2.67	0.33	1.05
P6	16;3.5	3.1	0.4	1.28
P7	26;4	3.82	0.18	0.57
P8	43;4	3.7	0.03	0.1
P9	50;3.5	3.06	0.44	1.4
P10	54;3	2.53	0.47	1.5
P11	59;2	1.7	0.3	0.96
min			0.03	0.1
max			0.47	1.5
avrg			0.31	0.98

Comparison

Applicator	Min offset in mm	Max offset in mm	Average offset in mm	Tolerance in mm
A 1H	0.17	1.37	0.71	±0.71
A 2H	0.18	1.70	0.79	±0.53
A 4H	0	2.03	0.48	±0.79
5H	0.07	1.72	0.68	±1.03
3H	0.2	1.98	0.96	±0.99
4H	0.11	1.21	0.59	±1.1
2H	0	0.48	0.28	±0.72
1H	0.1	1.5	0.98	±0.83
Total	0	2.03 (2.82 with Tolerance)	0.68	±1.1

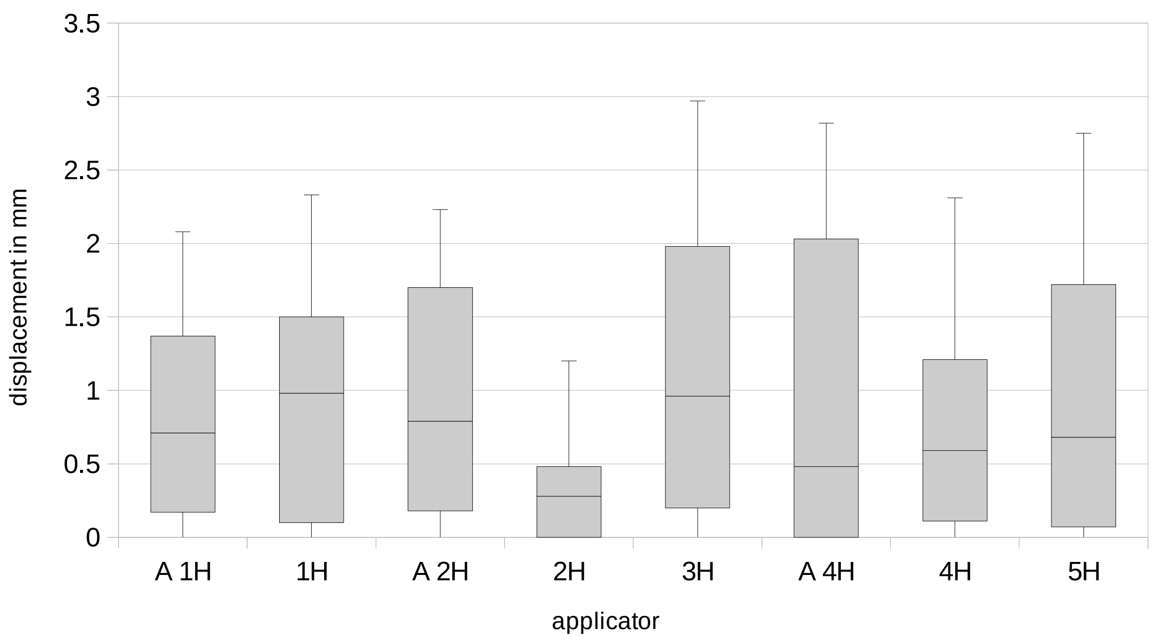


Figure 41: Applicator curvature accuracy

Figure 1 shows that the inaccuracies/displacements/offsets are more or less the same for each applicator. The maximum displacement is about 1.98 ± 0.99 mm. The average displacement is about 0.68 ± 1.1 mm.

Appendix E) CFMA treatment curvature inter-variance

Inter-variance of CFMA treatment curvature

Purpose: The objective of this test was to give an indication of the inter-variance of CFMA treatment curvature in order to validate the method of CFMA treatment curvature estimation by comparing the results with the estimated applicator curvature measurements.

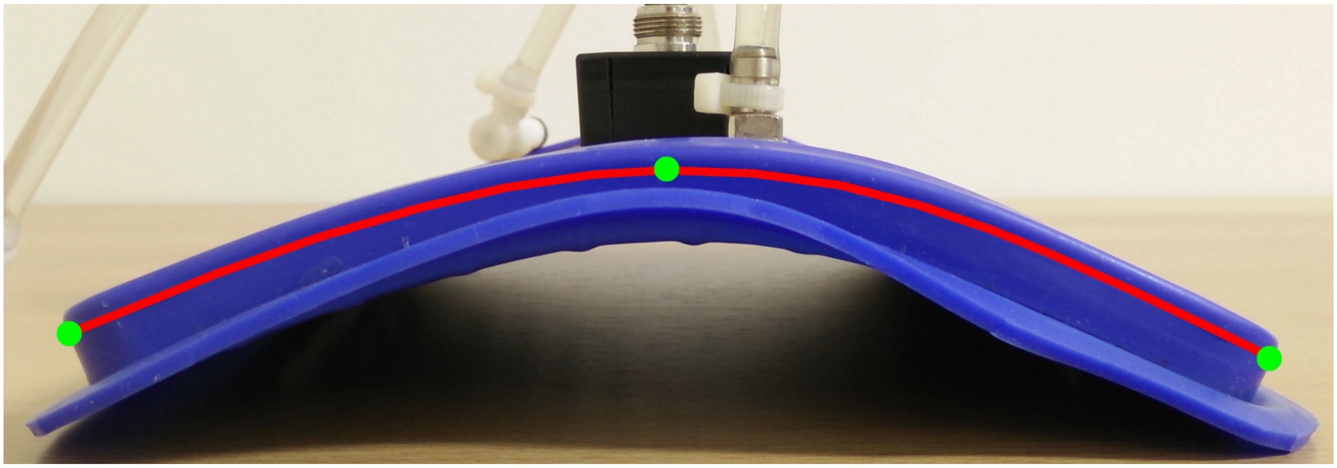
Methods and Materials: During the treatment period for one patient, photographs are taken after each treatment session. The photographs are all taken from the same position and angle relative to the applicator. The three points P1, P2 and P3, and a line following the treatment curvature are drawn. Then, all applicator lines are overlaid onto each other on a grid to visualize curvature differences. The largest differences are measured and the mean largest difference is calculated. Overlaying is done in two ways. At first, the first points (P1) are matched, later the curvature lines are shifted so that the variance is minimised.

Results: When overlaying is done by matching the first points (P1), a mean maximum difference relative to each other of 9 mm ± 1.17 was found.

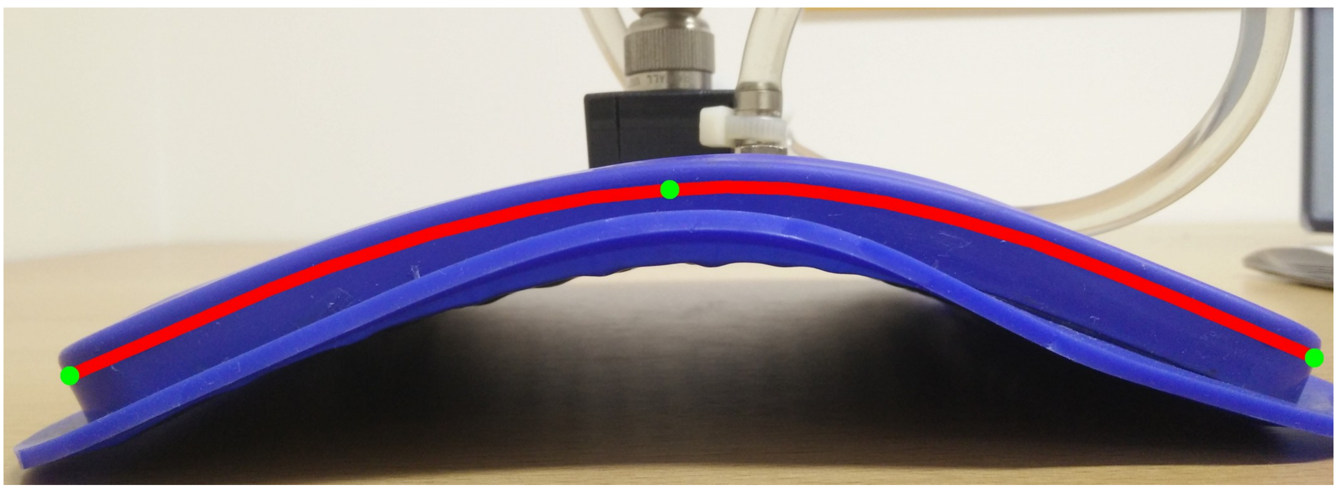
When overlaying is done by shifting the curvature lines to minimise the variance. A mean maximum difference relative to each other of 5.85 mm ± 1.17.

Conclusion: In the estimated applicator curvature measurements, a maximum variance of 1.98 ±0.99 mm is found. In the worst case scenario of this research, the mean maximum difference will be 5.85 - 1.17 = 4.68. The 1.98 + 0.99 = 2.97 mm variance found in estimated applicator curvature measurements is less than the inter-variance of CFMA treatment curvature. Therefore, using two independent second-degree polynomial functions is a valid way for describing CFMA treatment curvature.

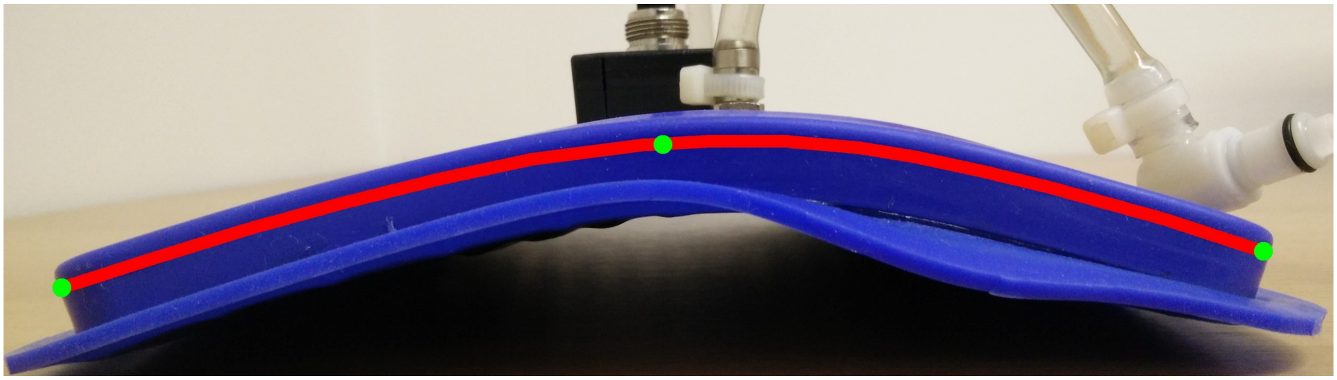
Treatment 1:



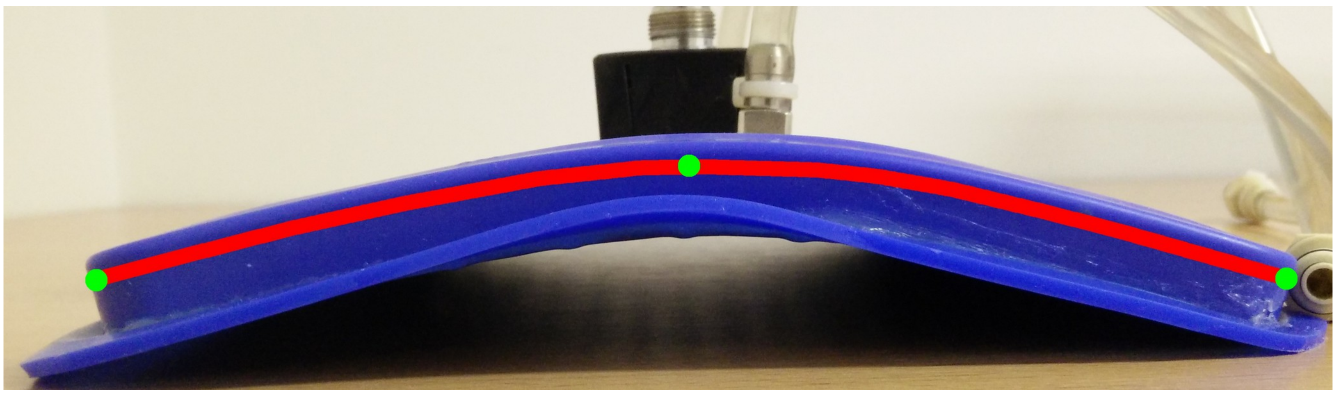
Treatment 2:



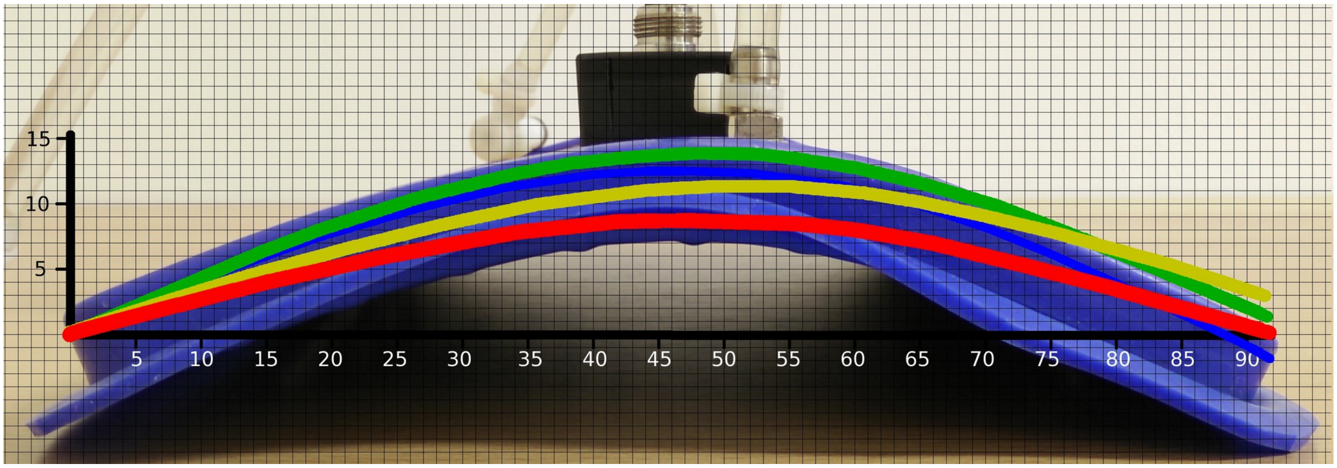
Treatment 3:



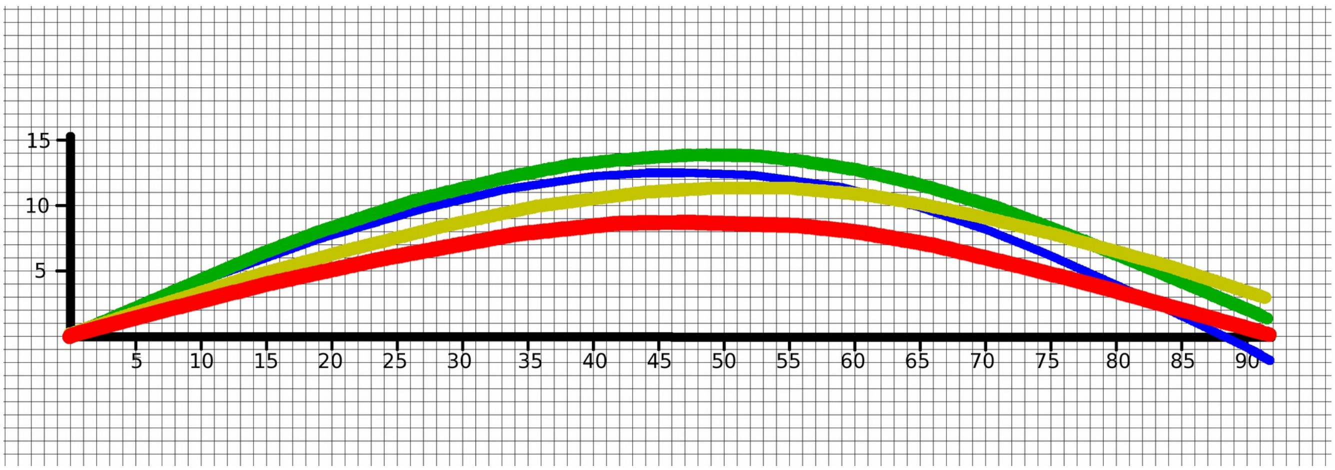
Treatment 4:



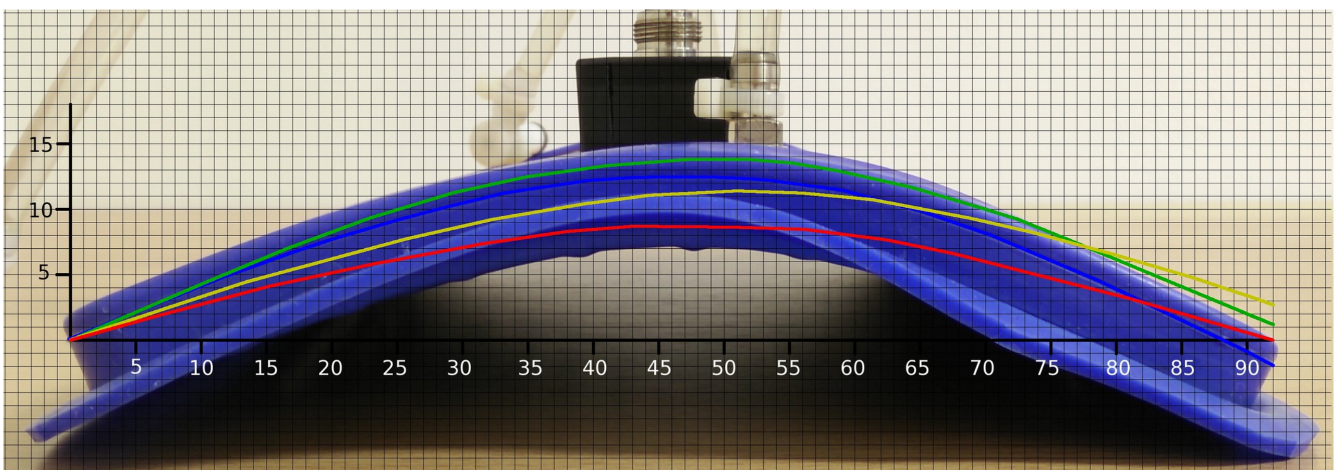
Comparison:



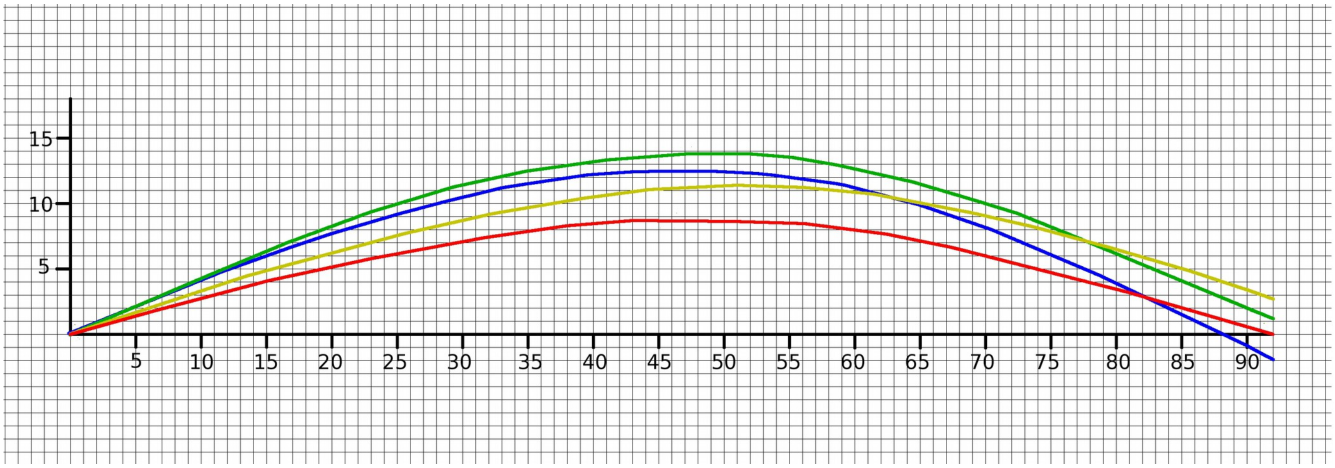
15
10
5
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90



15
10
5
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90



15
10
5
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90



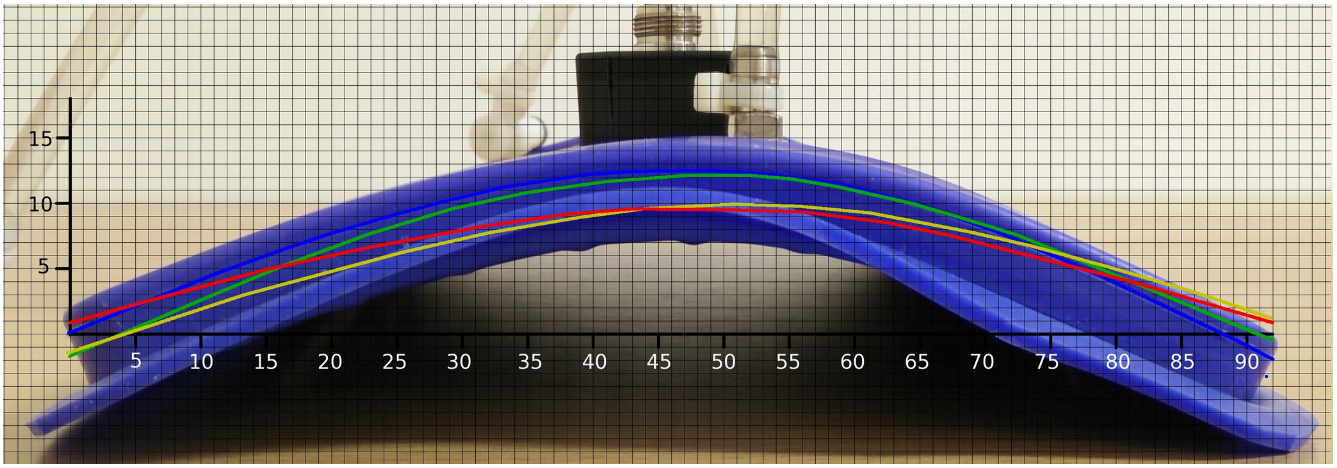
Scale: 1/2.34

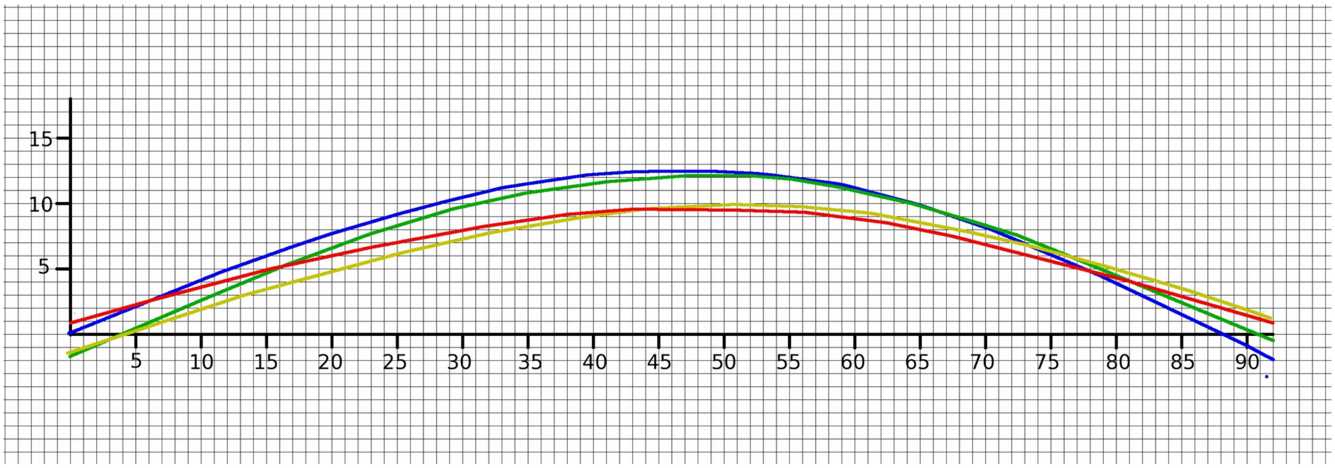
maximum variance: 12 mm ± 1.17 mm

maximum from original: 12 mm ± 1.17 mm

mean maximum difference from original: 9 mm ± 1.17 mm

Blue	9 mm ± 1.17 mm
Green	9 mm ± 1.17 mm
Red	9 mm ± 1.17 mm
Yellow	9 mm ± 1.17 mm
Average	9 mm ± 1.17 mm





Scale: 1/2.34

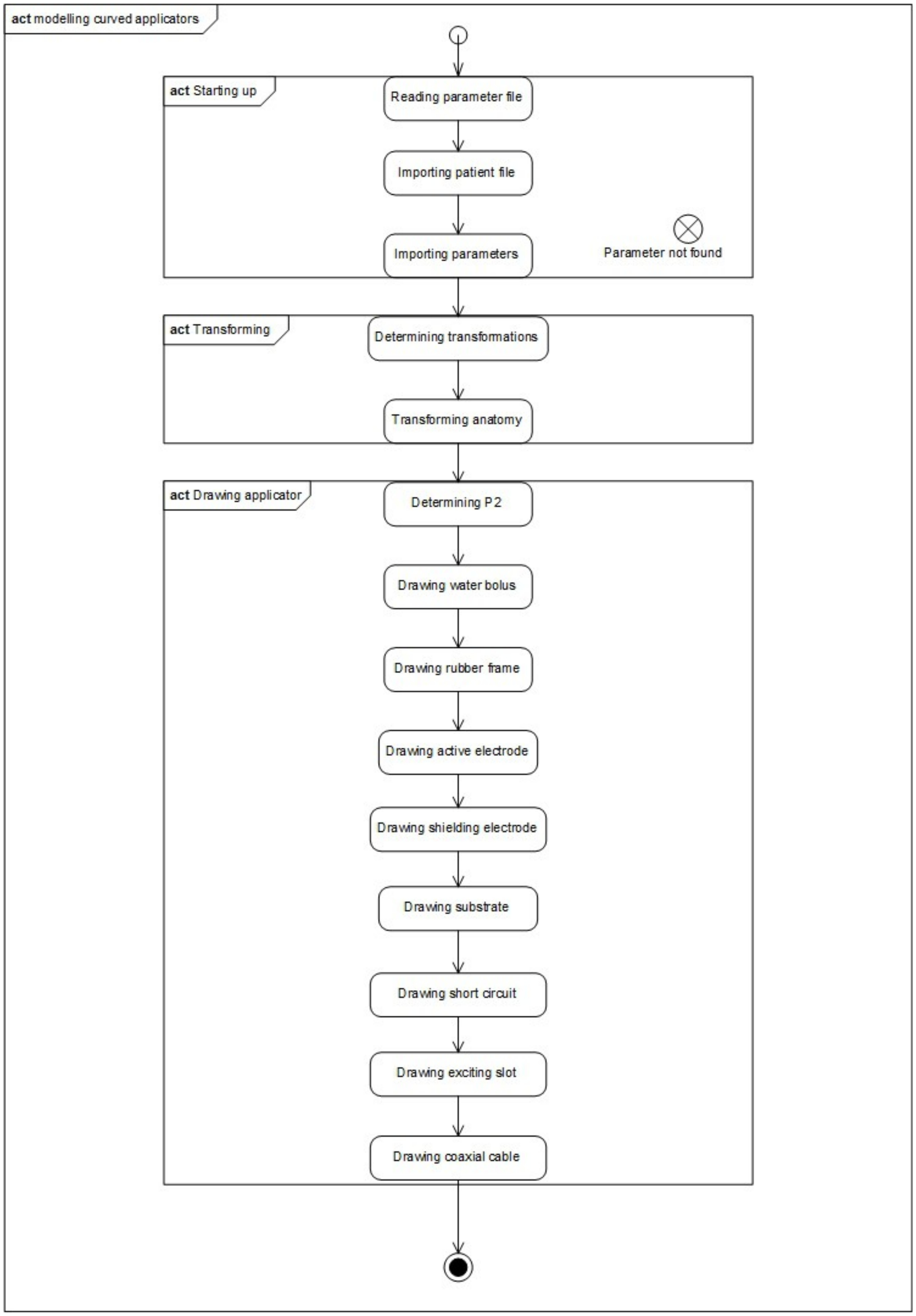
maximum variance: 7 mm ±1.17 mm

maximum from original: 7 mm ±1.17 mm

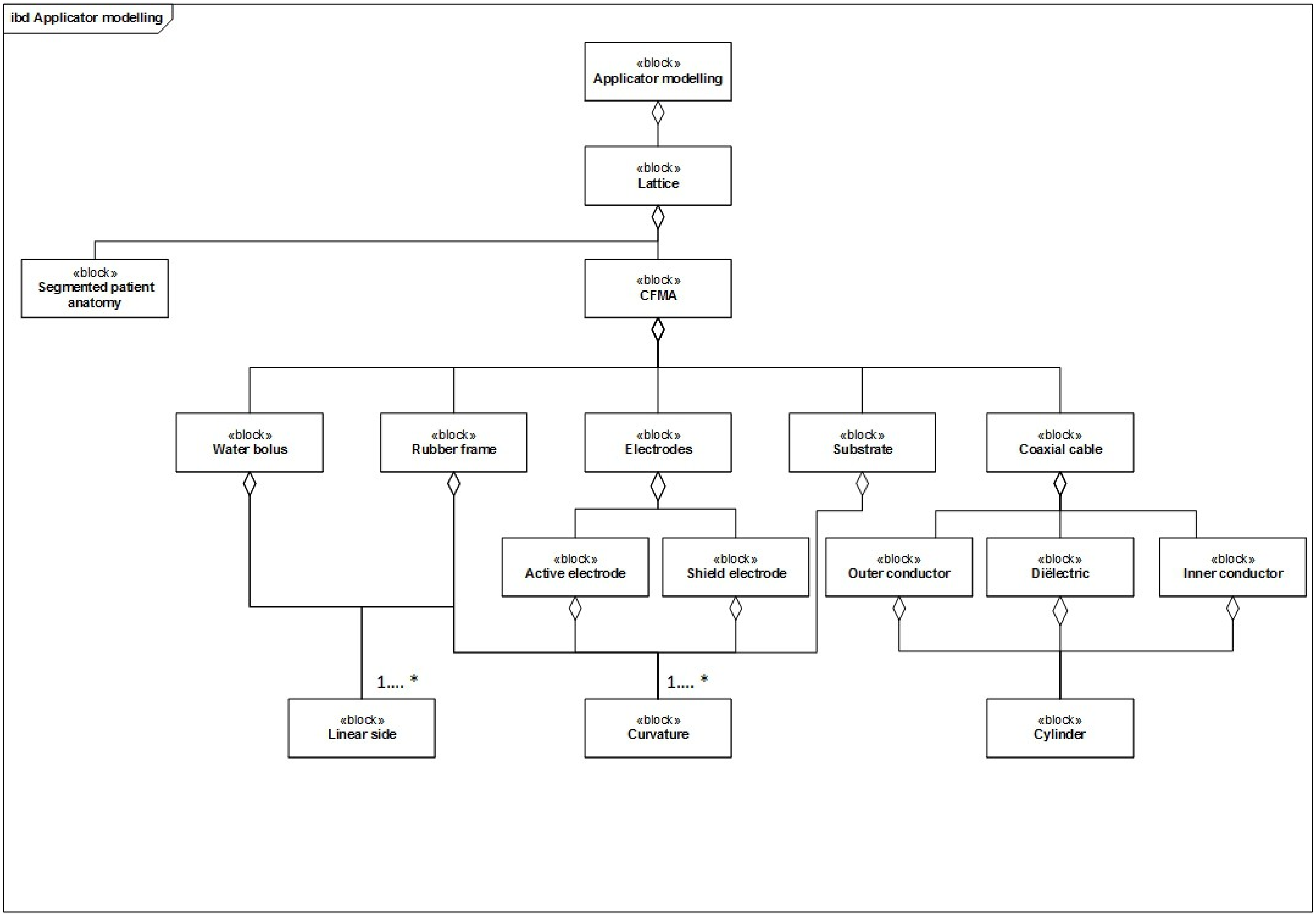
mean maximum difference relative to:

Blue	6 mm ±1.17 mm
Green	5 mm ±1.17 mm
Red	6 mm ±1.17 mm
Yellow	6 mm ± 1.17 mm
average	6 mm ± 1.17 mm

Appendix F) Activity diagram



Appendix G) Internal Block Diagram Applicator modelling



Appendix H) Use case diagram