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Towards a microwave hyperthermia system for head and neck tumors

by

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Always go too far, because that's where you'll find the truth.
A. Camus (1913-1960)

Abstract

Hyperthermia has shown the ability to enhance the performance of radiotherapy and chemotherapy in many clinical trials. The incidence of increased tissue toxicity as a result of high radiotherapy does, made hyperthermia as a safe method in combination with radiotherapy to enhance the treatment outcome. Although many clinical studies have shown the effectiveness of hyperthermia for treatment of head-and-neck (H&N) cancer, presence of large vessels, tissue transitions and critical tissues in head and neck pose therapeutic challenges for treatment of advanced tumors in this region. Moreover the application of hyperthermia to deep seated tumors in H&N region requires suitable heating equipment which was not available until recently.

In this thesis, a ultra wideband antenna has been designed, evaluated and built to act as the radiating element of microwave hyperthermia applicator. The time reversal focusing technique is used to target electromagnetic energy to the tumor. This focusing method is implemented by a 3D finite difference time domain based code for tumor models in head and neck.

The single antenna element is a modified bow-tie antenna with wideband characteristic over 430-1000 MHz and small size. The antenna size has been reduced considerably by immersion in a conical shape water bolus, while maintaining the radiation characteristics in the presence of human phantom. The specific shape and size of water container, wideband matching network between coaxial port and feeding elements of the bow-tie and addition of low-permittivity dielectric material to the bow-tie radiating arms are the other influential factors on final performance of the antenna.

The focusing ability of 3D time reversal technique was analyzed using tumor models in head and neck region of an anthropomorphic phantom. Two hyperthermia applicators were designed and used, one for the head and one for the neck. The 3D models of Head&Neck phantom together with phased array applicators were modeled in two electromagnetic solvers, CST microwave studio and an inhouse developed FDTD-based code.

Keywords: microwave hyperthermia, time reversal, wideband antenna, treatment planning, head and neck tumors.

List of Publications

This thesis is based on the following papers:

Paper I.

P. Takook, H. Dobšíček Trefná, J. Gellermann, M. Persson, "Compact self-grounded Bow-Tie antenna for UWB hyperthermia applicator", submitted to *IEEE Transactions on Biomedical engineering*.

Paper II.

P. Takook, H. Dobšíček Trefná, A. Fhager, M. Persson, "Evaluation of the 3D time reversal method for hyperthermia treatment planning in head and neck tumors", *Proceedings of 9th European Conference on Antennas and Propagation*, Eucap 2015, Lisbon, Portugal, April 2015.

Paper III.

P. Takook, H. Dobšíček Trefná, Xuezhi Zeng, A. Fhager, M. Persson, "A Computational Study of Time Reversal focusing Method for Hyperthermia Treatment Planning", *In manuscript*, 2016.

Other publications not included in the thesis:

1. H. Dobšíček Trefná, **P. Takook**, J. Gellermann, J. Yang, S. Abtahi and M. Persson, "Numerical Evaluation of Clinical Applicator for Microwave Hyperthermia Treatment of Head & Neck Tumors",*Proceedings of 7th European Conference on Antennas and Propagation*, Eucap 2013, Göteborg, Sweden, April 2013.

2. **P. Takook**, H. Dobšíček Trefná, M. Persson, "A compact wideband antenna for deep hyperthermia applicator", *28th Annual Meeting, European Society for Hyperthermia Oncology (ESHO)*, Munich, Germany, June 2013.

3. **P. Takook**, H. Dobšíček Trefná, M. Persson, ”A compact wideband antenna for microwave hyperthermia system”, *Proceedings of Medicinteknikdagarna*, Stockholm, October 2013.

4. M. Persson, A. Fhager, H. Dobšíček Trefná, **P. Takook**, Y. Yu, T. McKelvey, J. Karlsson, X. Zeng, H. Zirath, M. Elam, ”Microwave based diagnostics and treatment in practice”, *2013 IEEE MTT-S International Microwave Workshop Series on RF and Wireless Technologies for Biomedical and Health-care Applications (IMWS-BIO)*, Singapore, December 2013.

5. H. Dobšíček Trefná, J. Jonsson, B. Vessman, J. Wanemark, E Woxlin, A. Hjalmarson, L. Adelback, J. Gellermann , **P. Takook**, B. Lannering, K. Blomgren and M. Persson, ”Antenna applicator for microwave hyperthermia treatment of pediatric brain cancer”, *Proceedings of 8th European Conference on Antennas and Propagation*, Eucap 2014, Hague, Netherlands, April 2014.

6. **P. Takook**, H. Dobšíček Trefná, A. Fhager, M. Persson, ”3-D time-reversal method in microwave hyperthermia”, *29th Annual Meeting, European Society for Hyperthermia Oncology (ESHO)*, Torino, Italy, June 2014.

7. **P. Takook**, H. Dobšíček Trefná, A. Fhager, M. Persson,”Evaluation of 3D time-reversal focusing method in microwave hyperthermia treatment: head and neck tumors” *16th Nordic-Baltic Conference on Biomedical Engineering and Medical Physics & 10th Medicinteknikdagarna*, Göteborg, October 2014.

8. **P. Takook**, H. Dobšíček Trefná, M. Persson, ”Improvements in hyperthermia applicator design for heating head tumors”, *30th Annual Meeting, European Society for Hyperthermia Oncology (ESHO)*, Zurich, Switzerland, June 2015.

9. **P. Takook**, H. Dobšíček Trefná, A. Fhager, M. Persson, ”Performance evaluation of dipole versus modified Bow-Tie in annular phased array applicators”, *Progress In Electromagnetics Research Symposium, The 36th PIERS*, Prague, Czech Republic, July 2015.

10. A. Fhager, H. D. Trefná, **P. Takook**, Y. Yu, T. McKelvey, J. Karlsson, X. Zeng, M. Elam and M. Persson, ”Microwave Technology in Medical Diagnostics and Treatment”, *2015 IEEE MTT-S International Microwave Workshop Series on RF and Wireless Technologies for Biomedical and Healthcare Applications (IMWS-Bio 2015)*, Taipei, September 2015.

11. **P. Takook**, H. Dobšíček Trefná, M. Persson, ”Designation of optimal frequency for multi-frequency phased array”, *12th International Congress of Hyperthermic Oncology (ICHO)*, New Orleans, Louisiana, April 2016.

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Contents

CHAPTER 1

Introduction

Cancer is among the leading causes of death worldwide. There reported 14 million new cases and 8.2 million cancer-related deaths worldwide in 2012 [1]. The standard cancer treatment methods include surgery, radiation therapy and chemotherapy. Surgery is the oldest cancer therapy, which is usually combined with other modalities to improve the treatment of tumors. The reason is that removal of the tumor for many patients is not sufficient to avoid the cancer recurrence. Radiotherapy, on the other hand is not very effective at lower doses and could fail in treatment of bulky tumors. Moreover limited dose tolerance of some normal tissues can put them at risk and results in failure of the tumor treatment. This treatment modality may lead to late complications or increasing the risk of developing other cancers. Moreover it was suggested that chemotherapy might eradicate the tumor if it is given in early stages of disease when the metastasis is undetectable [2].

The disappearance of tumor after high fever was first reported more than a century ago [3]. Since 1960s hyperthermia attracted a considerable interest in cancer therapy. In hyperthermia treatment tumors are heated selectively to temperatures above 40°C while healthy tissues are kept below tissue-dependent critical temperatures [9]. This makes tumor cells more sensitive to chemo or radiotherapy and consequently have a positive impact on the treatment outcome without any toxicity. Comparison of radiotherapy alone with combined thermoradiotherapy in several clinical trials have shown the benefits of hyperthermia in terms of local control and survival in e.g. recurrent breast cancer, cervical carcinoma or H&N tumors [13][5][4][14].

In treatment of advanced H&N tumors, standard radio-chemotherapy generally results in a 5-year survival rate of 20-65% which depends on the stage and location [32]. Other studies show that combined RT and chemotherapy in H&N results in 8% increase in 2-years survival and more recently 4.5% increase in a 5-years survival was reported[15][16]. In addition the toxicity level in this type of tumor is severe and increases with radiotherapy doses. For example increasing swallowing complaints and decreasing saliva production have been observed with high radiation doses. It is shown that hyperthermia has the ability in enhancing the cells sensitivity to radiation and drug. In 1997, Amichetti showed the advantages of local hyperthermia in combination with hyperfractionated radiation in the treatment of advanced squamous cell carcinoma of the head and neck. Except mild acute local toxicity, no severe late side effects were observed in this study [6]. Benefits of adding hyperthermia to standard radiotherapy for patients with locally advanced cervical carcinoma was also shown in the study by Franckena et al [7]. In the first randomized phase 3 trial by Issels et al, regional hyperthermia has shown to increase the benefits of chemotherapy for localized high-risk soft-tissue sarcoma [8].

Considering hyperthermia abilities in combination with radiotherapy, we can expect enhancement in treatment outcome of head and neck (H&N) tumors. This enhancement is a result of increased RT dose in the tumor and decreased RT dose in the areas at risk. The application of combined RT plus hyperthermia to deep-seated tumors in H&N region requires appropriate heating equipment, which are able to deliver adequate thermal dose to this region of large vessels. Most clinical hyperthermia systems utilize electromagnetic fields or ultrasound for radiation into a target volume. Figure 1.1 shows the main components of a hyperthermia system, a PC for treatment planning, an amplifier system, antenna applicator and thermometer. A generator is used to supply the power of EM or US radiation, to be delivered to the patient by an applicator. The EM fields used to heat body tissues are in the frequency range of 0.5 MHz to 2.45 GHz, covering low frequencies to microwave range. Different type of applicators were developed for this frequency range such as waveguides, dipole antennas or coils. For many years capacitive electrodes and inductive coils were used at frequencies lower than 40 MHz [31]. At frequencies larger than 400 MHz, waveguide applicators, horn, spiral and current sheet are some of the common clinically used examples. A water bolus is usually placed between the antennas and body surface to emit microwaves or radiowaves into the tumors. The water bolus on body surface ensures the electromagnetic coupling into the body, improves the impedance match to the tissue and used as a method for cooling the skin and other superficial tissues. The bolus and cooling system, as parts of the applicator in Figure 1.1, are other components of a hyperthermia system. The interaction of the generated EM fields with body tissues, governed by the complex tissue permittivity, results in EM heating inside the tissues[2].

Hyperthermia treatment planning is used to derive a 3D patient model and optimizing the treatment parameters by electromagnetic and temperature simulation to result in the best temperature pattern in clinics [18]. The process of hyperthermia treatment planning is explained in chapter 3 in more details. Thermometry is used to measure the temperature of the target during the treatment in order to evaluate the quality of clinical outcome. Invasive thermometry systems consist of temperature sensors and provide temperatures from a limited volume of the target. Among the non-invasive thermometry methods, magnetic resonance thermometry has been clinically proven to be a reliable technique for real time temperature monitoring [17].

Annular phased arrays are the most common type of applicators for regional hyperthermia in which deep-seated tumors are treated. In these applicators, it is possible to change the distribution of the absorbed power by adjusting the amplitude and phase of each antenna in the applicator. The optimal amplitudes and phases can be obtained during the treatment planning process. The desired focusing into the target is given by constructive interference of the radiated electromagnetic fields from the antennas, as shown in figure 1.2 [31].

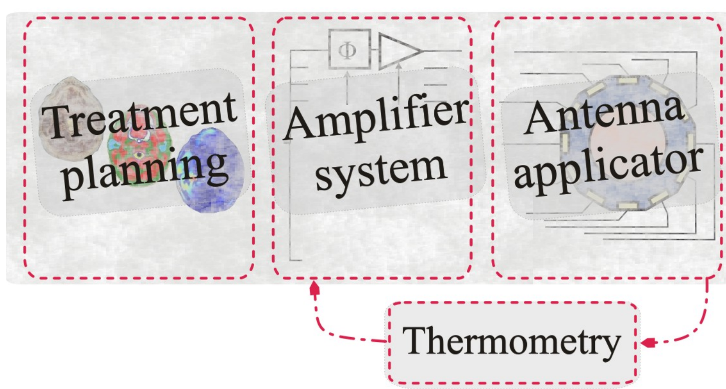


Figure 1.1: Main components in hyperthermia system

Several studies have shown that significant improvement in tumor power deposition can be given by increasing the number of the antenna elements or antenna rings [35][22]. Moreover the frequency of operation to have the optimal power density pattern depends on the size and position of the tumor and also the size of the treated body region. For example, the frequency of 434 MHz was chosen in the work by Paulides et al [36] for treatment of H&N tumors while 70 MHz was the operational frequency for treatment of pelvic tumors [10][11]. Positioning of the patient respect to the radiating system is the other influential factor in enhancing the power deposition in the tumor. Despite these methods to increase the heat delivery in the tumors, there exist therapeutic challenges in treatment of deep-seated tumors in head and neck region due to its complex geometry.

Figure 1.2: Conceptional design of H&N applicator

1.1 The aim of this thesis

The aim of this thesis is to develop a hyperthermia system for treatment of head and neck tumors. The thesis describes the design and development of a hyperthermia applicator which has the ability of focus-size adjustments by adaptation of power density pattern. This is achieved by changing the operating frequency of the antenna elements with wideband performance over the required range of frequencies. To achieve focused heating in the target, time reversal focusing method is employed in hyperthermia treatment planning.

The thesis is organized as follows: Chapter 2 introduces the requirements on microwave hyperthermia systems for deep-seated tumors and chapter 3 reviews the simulation techniques in hyperthermia treatment planning with emphasis on time reversal focusing technique. Brief summaries of the papers are given in chapter 4 while concluding remarks and discussions of future work are presented in chapter 5.

CHAPTER 2

Deep hyperthermia applicators

The ultimate goal of the project is to design and develop a hyperthermia applicator for head and neck tumors. The applicator must be able to effectively heat both superficial tumors and tumors located deeply in the H&N region. Until recently most of the hyperthermia application in H&N area was just restricted to superficial regions due to lack of deep HT applicators. For deep heating in the body trade-offs has to be made in terms of penetration depth, focal size and size of the target. The most common approaches use EM fields between 8 and 140 MHz with large wavelength compared to the tumor and body size. The problem in these applicators is limited control over the focused power density. Despite this problem, capacitive applicators have been used to raise tumor temperatures to 42°C in both superficial and deep-seated tumors with minimal adverse effect [19]. Application of phased arrays for HT treatment of superficial H&N tumors was investigated earlier in 80s [20][21]. HYPERcollar, a phased-array of 12 antennas, was the fist applicator which was developed for deep heating in H&N region [33]. Recently HYPERcollar3D has been developed by the same group with more focus on the integration of microwave hyperthermia into the clinic [34]. In this chapter, the characteristics of the present deep HT applicators are reviewed and followed by our approach in developing a hyperthermia applicator for head and neck tumors.

It has been shown that for adequate heating of deep seated tumors, applicators with many antenna elements are required [35]. The number of antennas is one of the influential factors on power deposition pattern in tumor and surrounding healthy tissues. The typical phased-array set up for deep hyperthermia application is a circular or elliptical array of antennas arranged around the body part to be heated and matched to the patient by a water bolus. The water bolus, placed between the applicator and the patient's body surface, is used to facilitate power transfer from the applicator to the body. High values of power transmission and low values of power reflection are indicative of a good coupling efficiency between the applicator and the patient.

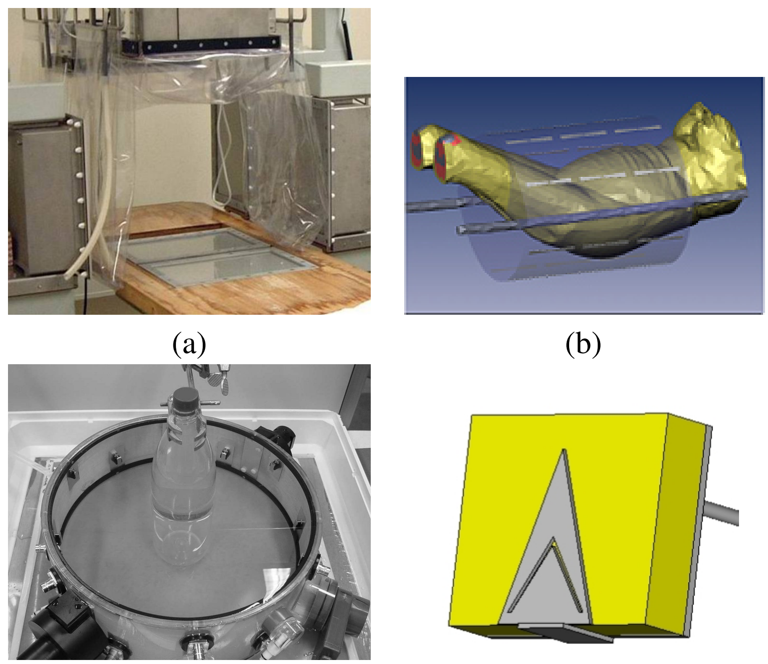
2.1 Single antenna element

The most common antenna type in deep hyperthermia applicators are waveguide or dipole antennas. Since small-size antennas are desired, antennas are either filled with water or immersed in water to be reduced in size. In early designs waveguides are filled with water, however they are large and heavy with narrow bandwidth [23]. AMC-4 and AMC-8 are one of the existing deep hyperthermia systems which composed of 1 ring or 2 rings of 4 waveguides at 70MHz, respectively. Due to the low operational frequency, these applicators provide a large penetration depth and the focus size is usually larger than the size of the tumor which is not desired. BSD2000 is the commercial deep hyperthermia system where dipole antennas are employed as radiating elements at the frequency range of 75 to 120 MHz [26]. The modified circumferential applicator, Sigma-Eye, composed of 24 dipoles arranged in 3 rings of 8 antennas [25]. The more number of antennas in this applicator compared to the older version, Sigma-60, has led to higher thermal dose in the tumor. A later version of the Sigma-Eye applicators is compatible with magnetic resonance imaging to allow MR scans of the patient and noninvasive monitoring of deep tissue temperature [27].

The drawback of dipoles are high amount of power absorption as a result of their matching networks [37]. Moreover omnidirectional pattern of dipole antennas makes them more prone to cross coupling effects. Patch antennas have also got lots of attention for hyperthermia application due to their lightweight and no need for matching networks, figure 2.1. A probe-fed patch antenna has been designed for the first clinical head and neck phased-array applicator for operation at 433MHz [38]. The antenna with bandwidth of 20 MHz at -15 dB reflection coefficient, delivered efficient power coupling into the water bolus by using water as substrate material.

In a study in our group, a patch antenna of about 170 MHz bandwidth was designed for a wideband hyperthermia system, figure 2.1(d). The patch antenna of triangular shape with dimensions of 37 mm by 25 mm was excited by a probe feed and immersed in a water bolus to decrease the operating frequency. The analysis of the single antenna showed a wideband performance beyond the bandwidth only by using waterbolus of different permittivities which was a constraint for clinical practice [47]. A desired bandwidth of 750 MHz was achieved later by the stacked ϕ-slot design with two shorting pins, but the radiation pattern split above 750

MHz was not desired. In this thesis modified bow-tie antennas are employed as antenna elements in hyperthermia applicator. Characteristics of this antenna have been compared with those of dipole, patch and waveguide in table 2.1.



(a) (b) (c) (d)

Figure 2.1: Antenna elements for hyperthermia applicators,(a) Waveguide antenna (b) Dipole antenna (c) Patch antennas in a 2-ring measurement set-up [38] (d) Triangular patch antenna [47].

2.2 Bolus

Water bolus is an important part of hyperthermia applicator with profound effect on heating pattern of the antennas. In most cases the space between the applicator and the patient is filled with water bags of low temperature to improve coupling to the patient, reduce stray fields and control the skin temperature. This is a closed water bolus system. the efficiency of power coupling between the applicator and the patient can be changed with thickness and shape of the water bolus. Open water bolus system has been used in Coaxial TEM applicators [39]. In this applicator designed for treatment of deep tumors in pelvic region, patient was surrounded by water from toes to upper chest. This approach provided optimal skin cooling without the pressure from water bolus weight on patient. The major disadvantage of

Table 2.1: Typical characteristics of different antennas in a hyperthermia applicator.

	Waveguide	Dipole	Patch	Our antenna	Desired characteristic
S_{11}	<-10 dB	<-10 dB	<-10 dB	≊-10 dB	≤-10 dB
Radiation pattern	Directional	Omni directional	Semi directional	Directional	Directional
Bandwidth	few MHz	more than few MHz	≊ 20 MHz	≊ 570 MHz	600 MHz
Matching circuit	No	Yes	No	Yes	No
Polarization	Linear	Linear	Linear	Linear	Linear

this concept is limited access to the patient during the treatment as well as significant losses. The open water bolus system concept has been used in a regional applicator design for pelvic tumors[40]. In this system patient in a bent posture in a bathtub was surrounded by a submerged elliptically-shaped annular array antenna. In AMC-4 system with one ring of 4 waveguides, waveguides and water boluses cover a large area of the body which is not ideal for short patients [10]. In early works of head and neck applicator design, cylindrical set up of antennas were considered in infinite water bolus. The infinite water bolus later modified to a closed water bolus in HYPERcollar applicator [33] where bolus is inflated with stilled water and water has the ability to circulate.

In today's hyperthermia systems, the desired water bolus characteristic is its integration with the antennas in a single mechanical structure. This can provide easy positioning of the applicator around the target. The predictability of water bolus shape is also an important factor affecting the treatment planning performance. In HYPERcollar3D which is in use since 2014, the bolus shape predictability was improved by splitting the water bolus into an inner flexible section attached to the body and an outer stiff part where the antennas are immersed [34], such that water bolus has the ability to conform to skin contours.

2.3 Our approach

Our approach in designing an antenna applicator to heat both deep and superficial tumors is adding the ability of switching over multiple frequencies in the desired frequency range. This ability enables us to reach the centimeter-scale spatial resolution which is not achievable at lower frequency ranges. Thus the antenna elements in our applicator should be designed to have a wide-band performance. Other desired characteristics for antennas are the low reflection coefficients, high penetration ability and high effective field size over the whole band. Moreover, to be able of increasing the number of antennas in multi-ring applicators, the antennas of small size are required. Finally the antenna elements needs to be compatible with the magnetic resonance device which is required for non-invasive thermometry [49].

In this thesis, we present bow-tie antenna with wide-band performance and stable radiation characteristics over the frequency range of 430-1000 MHz. To reduce the size of antennas at lower frequencies in the range, the single antenna is immersed in water. The specially designed shape of water bolus plays a significant role in improvement of heating efficiency. In addition to limited-size water bolus of antennas, an extra water layer between antennas and patient is used for direction of electromagnetic energy into the body and cooling down the body surface during the treatment. More details on design and analysis of the antenna is presented in the first paper.

CHAPTER 3

Hyperthermia treatment planning

Hyperthermia treatment planning is a process that begins with obtaining patient model and creates a set of quality indicators to maximize the treatment quality by electromagnetic or thermal modeling [18][50]. Figure 3.1 illustrates the HTP process which begins with determining the geometry and tissue properties of the related body part. The computed tomography (CT) or magnetic resonance (MR) images of the related body part are segmented to give an accurate, patient-specific modeling. The electrical and thermal properties are then assigned to each tissue. In the next step, the power density (PD) and SAR distribution is computed using a combined model of the applicator and patient. Besides an accurate patient model, the precise applicator model is necessary for the quality of the treatment plan. The applicator modeling includes physical geometry of the applicator, water bolus as well as modeling the antenna excitation and accurate meshing. After determination of PD, temperature distribution can be predicted considering physiological conditions such as perfusion. Finally optimization methods are employed to maximize the power distribution or temperature in the tumor while minimizing it in remaining healthy tissues.

The most common numerical techniques in electromagnetic modeling are finite difference time domain method (FDTD) and finite element method (FEM), used to compute the electromagnetic fields generated by antenna applicators. FDTD is formulated on a Cartesian grid and it discretizes Maxwell's equations in the time domain. In FEM, the interested domain is subdivided into small sub-domains and the field solution is expressed in terms of a low-order polynomial on each of these sub-domains. FEM is efficient in terms of the cell numbers but mesh generation in this method is time-consuming. On the other hand, FDTD is simple to perform and needs less memory when dealing with large computational domains. Mesh generation is also simple in FDTD and its parallel nature makes it suitable for acceleration techniques.

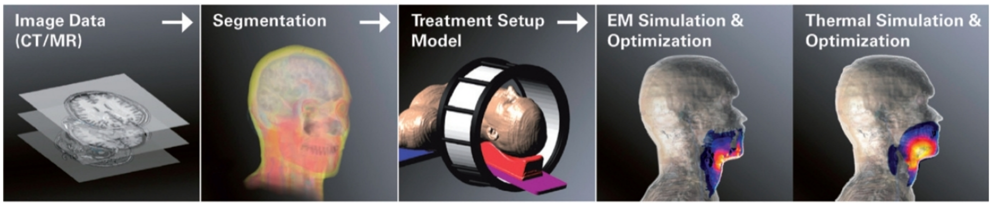


Figure 3.1: Process of hyperthermia treatment planning using electromagnetic simulation and optimization, [50].

3.1 Patient modeling

A strong dependence of power density and temperature distribution has been identified on 3D patient modeling. To derive 3D patient models, segmentation algorithms are required to delineate tissues from CT or MR data. The tissues are often manually segmented by clinicians in a time-demanding process. In order to speed-up the process, the automatic segmentation tools have been developed. Recently an automatic segmentation algorithm for CT images of the head and neck has been presented and evaluated which improves reproducibility and reduces the time of segmentation [46].

Although current clinical practice in hyperthermia treatment of head and neck is just based on CT images, magnetic resonance imaging results in higher soft-tissue contrast over CT. Current studies investigate the use of MRI in addition to CT for patient modeling in H&N hyperthermia treatment planning [42].

Numerical techniques are used to solve the Maxwell equations in order to calculate the internal electric fields within the body in hyperthermia treatment. To facilitate the use of the dielectric data in Maxwell equations, it is better to express their frequency dependence as parametric models. The characterization of dielectric properties of biological tissues was comprehensively reviewed by Foster and Schwan [51]. In the literature review by Gabriel et al, dielectric properties of biological tissues were extracted from literature and presented in a graphical format [52]. These dielectric properties were characterized experimentally in the frequency range of 10 Hz to 20 GHz [53]. A parametric model was then developed to describe the variation of dielectric properties as a function of frequency [54]. The dielectric spectrum of a tissue is characterized by three main relaxation regions and other minor dispersion. Each of these relaxation regions in its simplest form is expressed by the so called Debye expression as a function of angular frequency. Hurt also modeled the dielectric spectrum of muscle by the summation of five Debye dispersion and a conductivity term [55]. Accounting for the dispersion expansion, the Cole-Cole equation introduced as an alternative to the Debye equation [56][57]. Therefore multiple Cole-Cole dispersion is more appropriate to describe the spectrum of a tissue:

$$\hat{\varepsilon} = \varepsilon_\infty + \sum \frac{\Delta\varepsilon_n}{1 + (j\omega\tau_n)^(1 - \alpha_n)} + \frac{\sigma_i}{j\omega\varepsilon_0} \tag{3.1}$$

Dielectric properties of tissues are changing between different patients, especially in breast and brain [44]. The effect of this variation on the SAR of deep phased array applicators is found to be less than 10% [45].

3.2 Optimization techniques

3.2.1 Power density based optimization

In phased array systems, the most common type of deep hyperthermia applicators, the focusing into the target can be achieved by constructive wave interference of the electromagnetic fields radiated by antenna elements. Moreover hot spots which are often caused by electric field maxima at boundaries with high dielectric contrast, need to be minimized. This is usually done by different optimization methods among them are generalized eigenvalue method [59][60], genetic algorithm [62] or particle swarm optimization followed by line search[61].

Optimization process begins after calculation of the electric fields. In optimization of the power density (PD) or specific absorption rate (SAR), the amplitudes and phases of the sources are computed to give high PD/SAR in the target and low PD/SAR in healthy tissues. Considering a phased array of N antennas, the SAR distribution at voxel r is computed as:

$$SAR(r) = \frac{\sigma(r)}{2\rho(r)} |\sum_i^N E(r)_i V_i|^2 \tag{3.2}$$

where $E(r)_i$ is the E-field for antenna i, σ(r) and ρ(r) are conductivity and density at position r, and vector V is a complex vector showing the amplitudes and phases of each antenna.

In 1991, Sullivan presented a mathematical method for treatment planning in deep regional hyperthermia using Sigma 60 applicator [58]. To accelerate the computationally intensive optimization, he took advantage of the superposition of E fields while dividing the whole computational domain in 4 quadrants. He used the impulse response method where one computer run was required to find the E fields at frequencies of interest.

Generalized eigenvalue method has been used as a fast optimization method to find amplitudes and phases of phased-arrays in regional hyperthermia [60]. In this work, based on the basic equations for the electric field, power and temperature distribution, appropriate objective functions are defined for optimization of power density or temperature distribution. The defined functional for power density optimization compared the total absorbed power inside the tumor with the absorbed power in healthy tissues. Maximizing this functional led to the solution of a generalized eigenvalue problem. In the work by Bardati, the SAR optimization in a phased array for deep hyperthermia system was performed by maximizing the SAR in pathological locations and minimizing it in healthy organs [59]. The best array feed for each target was found by solving an eigenvector problem for several defined targets. The optimal set of excitation resulted from a trade-off of the best array feeds.

Quality indicators

The quality of a hyperthermia treatment is strongly affected by SAR in the target and SAR peaks outside the target, called hotspots. Therefore the SAR values in the target and hotspots are very influential in the analysis of SAR distributions. While the SAR in the tumor needs to be maximized to raise the tumor temperature, hotspots have to be minimized to prevent patient complaints during the treatment.

In a literature survey by Canters et al, several quality indicators have been evaluated in terms of their correlation to temperature increase in the tumor [63]. T_{50}, the median target temperature, was used to evaluate the SAR indicators for characterization and optimization purpose. The reason to choose T_{50} was its insensitivity to possible temperature deviation. Thus a high value quality indicator which had high correlation with T_{50} resulted in a high temperature. Based on this evaluation, two indicators have been found as the most appropriate indicators. $SAR_{hs-targratio}$ is defined as the ratio of the SAR exceeded in 1% of a region's volume and the median target SAR. This objective function used to compare the highest SAR values in healthy tissues to the tumor SAR, is the most useful for hotspots reduction and optimization procedure. SAR_{targ}, defined as the averaged SAR in the tumor, is most useful for comparison of absolute SAR values.

Consequently the Hot spot quotient ratio (HTQ), similar to $SAR_{hs-targratio}$, is also defined in Canters [70]:

$$\mathrm{HTQ} = \frac{\mathrm{SAR}(V_1)}{\mathrm{SAR}_{\mathrm{tumor}}} \tag{3.3}$$

Here $\mathrm{SAR}(V_1)$ is the average SAR in the first percentile of highest SAR values in healthy tissues and $\mathrm{SAR}_{\mathrm{tumor}}$ is the average SAR in the tumor. HTQ has been used as the goal function for optimization of SAR distribution in hyperthermia treatment planning and also to quantify the quality of SAR distribution [71]. As an objective function, it has been employed to maximize the SAR in the tumor and minimize it in healthy tissues.

3.2.2 Temperature based optimization

A temperature based optimization usually is based on optimization of power deposition before calculation of the temperature distribution. By incorporating nonlinear thermal models, extensive numerical simulations result in advanced combined approaches to solve the optimization and thermal modeling problems [68]. The common method for thermal modeling in hyperthermia treatment planning is Pennes' bio heat equation [65]:

$$c\rho\frac{\partial T}{\partial t} = \nabla.(k_{tis}\nabla T) - c_b W_b (T - T_{art}) + P \tag{3.4}$$

where c is the specific heat capacity, ρ is the tissue density, T is the temperature, t is the time, k is the thermal conductivity, W_b is the volumetric blood perfusion and T_{art} is the local arterial temperature. The deposited power density by radiators is shown by $P(Wm^{-3})$ and calculated from the total E-field distribution. Assigning different thermal properties to different tissues is used to model the heterogeneity in tissue properties. Heat transfer between large vessels and tissue and direction of blood flow are not considered in this model which can lead to inaccuracies in temperature evaluation. The most common numerical method for implementation of the PBHE is based on FDTD method. Since the PBHE is an approximate model, several modifications have been suggested for PBHE considering temperature dependent non-linear effects on thermal tissue properties. One of this modification is to use temperature dependent parameters [66]. In the other modified PBHE model, effective conductivity, k_{eff} is incorporated as a function of perfusion and an empirical factor [66].

To model discrete vasculature, a complex thermal method (DIVA) has been developed which describes vessels as 3D curves [64]. Complexity in modeling 3D vessel networks results in long computation times and makes this method impractical for clinical application. New methods have been developed for fast calculation of the steady-state temperature distribution and temperature-based optimization based on the DIVA model which are suitable for regular use in treatment planning [69][18].

Temperature-based optimization techniques to find the optimal phases and amplitudes of phased-array systems are more clinically suitable than power density based optimization. The reason is that they consider parameters such as thermal conduction and perfusion in the optimization process. The problem in this optimization is variations of thermal properties over time, in each patient and tissue and as a non-linear function of tissue temperature.

Quality indicators

Thermal dosimetry measures that are most often reported in literature include T_{90}, T_{10} and T_{50} as temperature parameters, cumulative time above 40°C, 41°C, 42°C and 43°C as time parameters, cumulative equivalent minutes at 43°C (CEM43) and cumulative equivalent minutes at 43°C for the T_{90} temperature as thermal dose parameters[72]. Here T_{90} is defined as the tissue temperature exceeded by 90% of all temperature measurements; T_{50} is the temperature which 50% of the measured points in tumor exceed and T_{10} is the temperature which 10% of the measured points in tumor exceed. In a proposed thermal dose relationship, it was shown that for every 1°C rise in temperature above 43°C, cell killing doubles while cell killing is reduced by about one quarter for every 1°C below 43°C [73]. This resulted in the expressions for CEM43 and CEM43T_{90}. For example EM43°C for sensitive brain is about 30-50 minutes threshold for damage while for more heat-tolerant muscle this threshold is 240 minutes.

3.3 Time reversal method

Time reversal method is based on the time-symmetric property of the wave equation in a nondissipative medium [74]. The time-reversed process starts with the radiation of a pulse from a point-like source at position r_0. A cavity is surrounding the source on which the time dependence of field components are measured. In electromagnetics, time-reversed wave fields inside the volume of the cavity are obtained by time reversing the E-fields and radiating them from the cavity surface. This corresponds to the transformation of $E(r,t) \rightarrow E(r,T_0 - t)$. These time-reversed fields are back propagating by monopolar or dipolar sources covering the surface [75]. Considering the source function as a Dirac distribution, the time-reversed electric field is given by:

$$E_{TR}(r,t) \propto G(r_0,r,-t) - G(r_0,r,+t) \tag{3.5}$$

where $G(r_0,r,t)$ is the causal and $G(r_0,r,-t)$ is the anticausal Green's function. The interference of the converging and diverging waves results in a focal spot with maximum size of $\lambda/2$. The focus size limit results from the Fourier transform distribution of the E-field which is proportional to the imaginary part of the Green's function:

$$G(r_0, r, \omega) = \frac{e^{-jk\|r-r_0\|}}{4\pi\|r-r_0\|} \tag{3.6}$$

and

$$\mathrm{Im}G(r_0, r, \omega) \propto \frac{sin(k\|r-r_0\|)}{\|r-r_0\|}, \tag{3.7}$$

where k is the wave number.

(a) (b)

Figure 3.2: The principle of the time-reversal method. (a) The recording step (b) The time-reversed step.

We use the principle of time reversal theory to achieve power absorption in the tumor volume. The advantage of the time reversal for hyperthermia treatment planning is in the speed of the method and being suitable for pulsed and continuous excitation. Unlike the traditional optimization methods, there is no need to calculate the E-fields of all the antenna elements in the applicator. On the other hand to minimize power absorption in healthy tissues, hot-spot reduction techniques are necessary to be incorporated in the process of treatment planning.

In the first step of the time reversal method, the modeling part, one or more sources are placed in tumor volume. The optimum position of the virtual source is where the maximum tumor coverage can be achieved. The simulated E-field are recorded by electromagnetic models of the antenna elements on the surface of the phantom or water bolus. In the second step, the treatment part, the antenna elements transmit the recorded field in a time-reversed order. The time-reversed signals are then focused in the position of initial sources in the tumor due to the time-symmetric property of the wave equation in a lossless medium.

In our previous work, the time reversal focusing method has been evaluated for hyperthermia treatment planning of 2D models of neck and breast [48]. The method was implemented by 2D FDTD algorithm and the 2D models were immersed in the background of water. The performance of the focusing method was evaluated by quantifying the power absorption distribution in tumor areas in terms of several parameters. The type of the antenna excitation, number of antennas in the applicator and frequency were the studied parameters. Although 2D time reversal method works quite well for 3D predictions [47][48], there are limitations in modeling more than one ring applicator in 2D modeling. This limitation can be obviated by 3D implementation of the time reversal method using FDTD algorithm.

CHAPTER 4

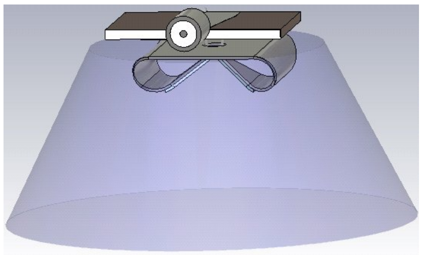
Summary of results

4.1 Paper I

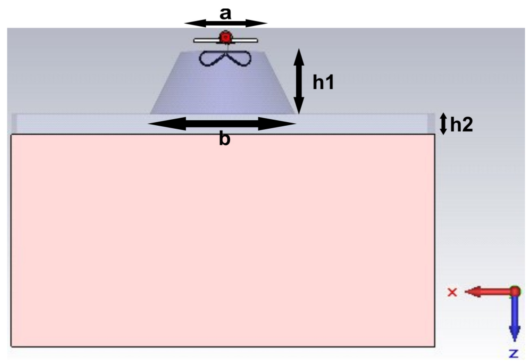
In this paper novel concepts in a self-grounded Bow-Tie antenna type design is presented to serve as the basis element in a phased-array applicator. The modified antenna with small volume of $24 \times 27 \times 11$ mm^3 has wideband characteristics over the frequency range of 430 MHz - 1 GHz which is not common in hyperthermia field. Besides a two-layer water bolus, addition of low permittivity dielectric layers on top of the antenna radiating arms is another novelty in antenna design.

The antenna structure composed of two parts, a wideband balun and the water bolus. Water bolus is used as the antenna immersion medium to decrease the size of the antenna. The water bolus has split in two parts, a surface water layer where the water can be circulated to control the temperature of the skin during the treatment, and the antenna water bolus where the antenna is immersed.

Among different antenna water bolus (AWB) shapes, the optimal shape was obtained by evaluation of the resulting reflection coefficient and SAR distribution of the antenna in a muscle phantom. The conical shape WB with acceptable PLD values and S_{11} parameters of the antenna is selected as AWB optimal shape. To find the optimal size of the AWB, the antenna performance was evaluated in terms of its reflection coefficients S_{11}, the effective field size (EFS) and the penetration coefficient pf_{TS}, for different values of the truncated cone parameters. The smallest possible AWB size which resulted in low reflection coefficients, high EFS and high pf_{TS} was selected as $a/2 = 20, b/2 = 35, h_1 = 30$ and $h_2 = 10$mm, Figure 4.1.



(a)



(b)

Figure 4.1: (a) The model of the self-grounded Bow-Tie antenna and (b) Antenna water bolus size parameters.

The improvement in antenna performance by addition of dielectric layers to the bow-tie radiating arms has been shown in terms of the surface current density, E-field distribution and the reflection coefficients of the antenna with and without the dielectric layers. It is seen that in presence of dielectric layers, higher surface current density on the antenna arms causes higher energy propagation into the muscle. Lower absolute value of the reflection coefficient was also observed with added dielectric layers in the conical shape of AWB.

The compatibility of the antenna with a MR scanner was investigated inside a 1.5 Tesla MR scanner. Magnitude MR images of the antenna covered by WB bags show that SMA connector with ferromagnetic material causes a large distortion in images and should be replaced with a non-magnetic one. In experimental validation of the antenna, the measured reflection coefficients of -9 dB or better are comparable with the simulation results in the frequency range 0.46 - 1 GHz. Finally the heating ability of the antenna was evaluated by measuring the temperature distribution in muscle phantom when the antenna was fed by 10 W power for 10 minutes. Maximum measured temperature by fiber optic probes was 6.5°C.

4.2 paper II

In paper 2, time reversal method for hyperthermia treatment of tumors in the head and neck area was presented. Two models of tumor in an anthropomorphic head and neck phantom were considered for our analysis. The applicator for the head tumor was modeled with 16 antennas arranged in 2 rings and the applicator for neck was a 1-ring applicator of 10 antennas, Figure 2 in the paper. The time reversal method was implemented in a 3D-FDTD in-house developed code where the virtual source and surrounding antennas were modeled once as point sources and once as half-wave dipoles. The excitation type of the antenna were selected as pulse and sinusoidal signal in the frequency range of 400-1200 MHz.

We studied the effect of the frequency, type of antennas and their excitation on the quality of treatment outcome in terms of some quality indicators. The computed performance indicators for UWB pulse and CW excitation showed that in the tongue tumor, pulse and single frequency excitation at 500 MHz performed approximately the same. However in the laryngeal tumor with smaller size, the advantage of using pulse was clearly visible at 500 and 800 MHz. For both tumor models, dipole antenna showed more absorbed power densities at tumor sites in comparison to point source antenna.

We performed the qualitative and quantitative analysis of power deposition in both tumor models and compared with the results of time reversal implementation in the commercial software (CST microwave studio). Despite the difference between CST and 3D code results for the tongue tumor, mainly due to different antennas types, the tumor coverage qualifiers for both tumors were comparable.

Finally the exact antenna model in the commercial software was compared with the approximate model in the 3D code. For this comparison the modified Bow-tie antenna and a half-wave dipole at 500 MHz were immersed in conical shape water bolus and were placed over a muscle phantom. The performance of the antennas were then compared in terms of $S_1 1$ and absorbed power densities in the muscle phantom. A wide-band performance was achieved by the Bow-Tie antenna over the frequency range of 0.4-0.9 GHz, in comparison to narrow bandwidth of the half-wave dipole. Moreover higher energy were delivered into the muscle phantom from the Bow-Tie antenna compared to the half-wave dipole.

4.3 paper III

Paper 3 presents the study to find the optimum frequency in hyperthermia treatment planning in terms of the antenna numbers in the applicator and tumor size and position. The optimum position of the virtual source in the recording step of the time reversal method is the other investigated topic.

Using time reversal as the focusing method, we found the antennas excitation at discrete frequencies in the range of 400-900 MHz, when they surround a homogeneous cylindrical phantom enclosing a spherical tumor. The analysis was performed for number of the antennas between 4-48 and tumor positions from the surface to the center of the phantom. Considering tumor with same dielectric properties as the phantom, power loss density values were computed in the phantom area. The analyses were performed in the middle cut-plane of the phantom to prevent long computational time with high number of the antennas. We decided the optimum frequency range for each tumor position and number of antennas based on the calculated aPA, the average power absorption ratio, and 50% tumor coverage. The computed aPA as a function of the number of antennas (NOA), frequency and tumor center position (TCP) is shown in Figure 6 in the paper. For each tumor position and number of antennas, we selected the frequency range with high aPA value and approximate 75% of $TC_{50\%}$.

In the second part, we carried out analyses in 3D model of an elliptical muscle phantom enclosing a spherical tumor of the same dielectric properties. For the applicator we considered the head applicator of 16 modified Bow-Tie antennas. Based on our previous analyses, the optimum frequency range for 16 number of antennas and all tumor positions is between 400-500 MHz. 50% tumor coverage was used to evaluate the heating efficiency at 400 and 500 MHz when tumor position were varied along the Y-axis of the phantom, from surface to center. As tumor center got closer to the phantom center, the position of the VS with maximum $TC_{50\%}$ got closer to the tumor center. For all the simulated frequencies, the maximum tumor coverage for the closest tumor to the phantom center, deepest tumor, was at tumor center position.

Finally the optimum position of the VS was found in realistic tumor models, deeply located in head. The analysis results in the tongue tumor showed agreement with the simple analysis results of the elliptical phantom. For larger and more irregular shape of skull-base tumor, one virtual source was not enough to reach an acceptable tumor coverage. Although the addition of another virtual source resulted in 20 times higher $TC_{25\%}$, clinically accepted tumor coverage is demanded.

CHAPTER 5

Conclusion

This thesis presents developments toward a microwave huperthermia system for treatment of head and neck tumors. Two of the main components in a hyperthermia system has been studied, the hyperthermia applicator and the hyperthermia treatment planning.

In the first paper, a wideband antenna is developed to be used as the single element of the phased array hyperthermia applicator. The antenna which is a self-grounded Bow-Tie was modified to present UWB operation over 0.43-1 GHz with acceptable radiation characteristic. The modification in antenna performance was achieved by immersing the antenna in water bolus and addition of dielectric layers on top of the antenna radiating arms. The evaluation of the antenna characteristic for hyperthermia treatment was performed by assessment of UWB impedance matching, transmission capability and effective field size. This evaluation resulted in finding the optimum shape and size of the antenna water bolus. The antenna was manufactured and experimentally validated on a muscle-like phantom. The measured reflection coefficients and radiation characteristics showed good agreement with the simulated results. Finally the MR compatibility test of the antenna inside a 1.5 Tesla MR scanner showed negligible image distortion by the antennas itself.

In the second and third paper, the focus is on the hyperthermia treatment planning. In both papers time reversal method which is based on constructive wave interference at tumor site, was used to find the amplitudes and phases of the antennas in the applicators. In paper 2, we evaluated 3D time reversal method for hyperthermia treatment of two tumor models in the head and neck. A 3D-FDTD based code was evaluated to find the effectiveness of its input parameters on the quality of the tumor treatment. The input parameters of the 3D code were the operational frequency, the type of the antenna elements and their excitation type. Computed hyperthermia quality indicators for two tumor models in tongue and larynx of a H&N phantom showed promising results in terms of the power deposition and tumor coverage.

In the third paper, which is a continuation of the second one, we studied a selection scheme for frequency and virtual source position in the time reversal method. For frequency selection, we assessed the computed average power absorption and tumor coverage in a spherical tumor model with same dielectric properties as the muscle phantom. The optimum frequency was then selected for a specific position and size of the tumor and specific number of antennas in the applicator. The selected frequencies from 2D time reversal analysis were in agreement with the optimum frequencies from 3D simulation results. To find the optimum position of the virtual source, a spherical tumor inside an elliptical muscle phantom was considered. The performance of treatment outcome for different VS positions was evaluated in terms of tumor positions, tumor sizes and frequencies in the range of 400-900 MHz. The behavior of the optimum VS position versus the tumor position was in agreement with the behavior of optimum VS position in realistic tumor models with simple geometry.

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