Interstitial microwave hyperthermia treatment investigations

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Abstract. Microwave ablation also called interstitial hyperthermia is a medical procedure used in the treatment of many cancers, cardiac arrhythmias and other medical conditions. With this medical therapy, an electromagnetic source (antenna) is directly positioned in the target tissue and a sufficient power is injected to necrosis the tissue. The aim of this study is to propose a design procedure and develop the associated tools, for determining the optimal shape, dimensions, type and operating frequency of antenna according to the target volume. In this context, a 3D numerical predictive model of temperature elevation induced by the electric fields and two benches for thermal and electrical tissues properties characterization have been developed. To validate the procedure and the different tools, an experimental bench test which includes interstitial antenna, external microwave generator, phantom that represents the target tissue and measurement system of temperature and electric field has been elaborated.

1. Introduction

Hyperthermia is a medical technique that uses heat to destroy or weaken a small volume of cells. Depending on tumor type and its position different hyperthermia techniques can be chosen by the patrician: interstitial, regional, external. This study focuses only on interstitial hyperthermia which is an ablative technique that consists to heat tissues locally to temperatures above 60 °C. Treatment time is typically less than 10 minutes. The aim of this technique is to destroy the target tissue, by increasing temperature and so burning the target site [1]. The heating energy can be generated by microwaves, ultrasound, radiofrequency (100 kHz to 500 kHz) or laser [2]. This technique is minimally invasive, well tolerated by the patient and relatively low price [3]. Our study focuses only on microwaves interstitial hyperthermia. In this context, an interstitial antenna operating between 433 MHz and 2.45GHz and connected to an external microwave generator is directly positioned in the tissue to destroy [4]. Principal challenge of interstitial hyperthermia is to destroy cancerous cells by focusing and controlling temperature elevation in target and to obtain a homogenous temperature distribution in the target without hot spots in healthy tissues [5]. To raise this challenge and design a robust system, it is necessary to have a predictive numerical model of the phenomena, to know biological tissues properties and to realize validation on ex-vivo tissues with temperature measurements [6].

The first paragraph presented the microwaves hyperthermia test bench used to characterize and design the monopole interstitial prototype probe operating. In the second part, procedure used to determine thermal and electrical tissues properties is exposed. Then, 3D numerical model based on the Pennes bio-heat equation, resolved with Finite Element (FE) and used on realistic 3D model of the human body is presented. Finally, future works and perspectives are discussed, and the areas for future research for electromagnetic ablation are outlined.
2. Interstitial antenna design
Validation procedure of the developed prototype probe and the various tasks associated are exposed.

2.1. Experimental equipment
The validation bench consists of a TTi TGR2050 2GHz synthesis RF generator operated at 915 MHz, coupled to an Aethercomm Model SSPA-1.0-2.5-50 amplifier and connected to the interstitial monopole antenna prototype probe. The amplifier needs a +28Vdc, 10A power supply to operate. Antenna is based on a UT-85 semi-rigid coaxial line. The interstitial antenna is immersed in phantom which has equivalent electrical tissues properties. Temperature measurements are realized with infrared camera and fiber optic thermometer.

2.2. Interstitial probe design
The metal tip length is deduced from equation (1), with \( \lambda \) the wavelength (m), \( c \) the celerity (m.s\(^{-1}\)), \( f \) the frequency (Hz) and \( \varepsilon_r \) the relative permittivity. The metal-tip antenna is fixed to 10 mm long.

\[
\lambda = \frac{c}{f \sqrt{\varepsilon_r}}
\] (1)

2.3. Phantom
Interstitial hyperthermia can be used in the treatment of stomach tumors [7], to represents this type of treatment an agar phantom with electrical properties of stomach biological tissues is realized. The constituents of the phantom are NaCl, agar-agar and water. The phantom permittivity is measured with the method presented in the paragraph 3.2, the results obtained are \( \varepsilon_r=66 \) and \( \sigma=1.3 \) S/m.

3. Physical characteristics of biological tissues
The method employed to realize thermal and electrical characterization of tissues properties is exposed. The different tools developed are implemented in C-language to reduce the execution time. To validate the characterization methods several test measurements are realized on muscle and fat pig tissues, because the properties of these tissues are similar to those of the human body.

3.1. Thermal properties: thermal conductivity, specific heat and mass density
This study determines, each parameter value, the uncertainties associated to parameters and parameters variability’s with temperature. Both mass density and specific heat measurements have been performed on standard devices, a pycnometer suitable for high viscous liquids and solids for the first one and a differential calorimeter for the second one. Thermal conductivity is identified using a flash method and by solving an inverse problem. Flash method is usually applied on solid materials. A brief excitation is applied on one sample face and the response in term of temperature is observed on the other side. The thermogram obtained during the excitation and temperature increase contains informations on sample thermal properties. Experimental thermogram is compared to a thermogram calculated with a program describing the sample behaviour on the experimental configuration. By minimizing a function, representing the sum of the quadratic discrepancy, between the experimental and theoretical thermogram, the investigated parameters: in our case the sample thermal diffusivity \( \alpha \) (m\(^2\).s\(^{-1}\)) can be identified. The minimization is performed by using an algorithm of identification based on a least square fit method which used the Gauss linearization procedure. While the flash method is usually employed on solid material, the experimental device has been adapted for measurements on liquids and soft materials [8]. Sample is situated in a cylindrical cell. By taking into account the experimental errors and models simplifications, uncertainties on thermal diffusivity have been found to be fewer than 4 %. Therefore, uncertainties on thermal conductivity which is linked to those on mass density and specific heat are fewer than 9 %. Measurements on flash method have been supply with measurements on hot wire method, which gives directly thermal conductivity values.

The campaign of test runs has been done on pig samples kept in sealed packages at -20°C. Mass densities measurements have been performed on samples of different pig at ambient temperature 25°C.
For example, the average density of pig muscle is about 1073 kg.m^{-3} and the average value of pig fat is about 951.3 kg.m^{-3}. The standard deviation for the measurements is 3 kg.m^{-3}. Specific heat measurements at different temperatures had pointed out the dependency on temperature of specific heat. On pig muscles from 31 °C to 37 °C, an increase of 16 J.kg^{-1}.K^{-1} per K is observed on initial value of 3482 J.kg^{-1}.K^{-1} and on fat vary from 37 °C to 45 °C, an increase of 28 J.kg^{-1}.K^{-1} per K is observed with a start value of 2763 J.kg^{-1}.K^{-1}. The table 1 summarized the thermal diffusivity \( \alpha \) measured and the resulting calculated thermal conductivity \( k_t \). The experiments presented have been performed on muscle and fat, seven day after the pig sacrifice. Hot wire method has been used to study the influence of fiber direction of tissues on thermal conductivity values. The experiences have been realized only on pig muscle tissues, the results highlight the thermal isotropic nature of muscle tissues.

### Table 1. Thermal diffusivity measured and calculated thermal conductivity.

| Tissues type | Temperature (°C) | Diffusivity \( \alpha \) (m^2.s^{-1}) | Conductivity \( k_t \) (W/m.K) |
|--------------|------------------|----------------------------------------|-----------------------------|
| Muscle       | 20.1             | 1.24e^{-07}                            | 0.464                       |
|              | 20.6             | 1.25e^{-07}                            | 0.467                       |
|              | 27.1             | 1.34e^{-07}                            | 0.499                       |
| Fat          | 20.0             | 1.14e^{-07}                            | 0.245                       |
|              | 25.4             | 9.59e^{-08}                            | 0.206                       |

3.2. Electrical properties: permittivity and electrical conductivity

The experimental bench is composed of a Vector Network Analyzer (VNA) Agilent E5071C, an open-ended coaxial dielectric probe and an optical fiber thermometer (figure 1). Dielectric probe is constituted of a semi-rigid coaxial line UT85 (figure 2). The reflection coefficient \( S_{11} \) parameter of the Middle Under Testing (MUT) is obtained with the VNA in the frequency range 0.5 to 4 GHz. Calibration procedure is realized with three trials: air, short circuit and ethanol. MUT temperature is monitored with an optical fiber thermometer. Figure 3 shows the geometry model of the probe.
In the model, the coaxial probe is considered as an infinite conducting ground plane at the aperture (z=0). MUT over the ground plane should be homogenous and isotropic. Due to coaxial probe dimensions, in the frequency range studied, assumption of a single propagating mode: principal TEM mode is justified [9]. So, the MUT permittivity identification is based on normalized aperture admittance model given by the equation (2) with $k = \omega \sqrt{\mu_0 \varepsilon_0} \varepsilon^*$ MUT propagation constant.

$$Y_{adm}^* \approx -i 2 \omega \varepsilon_0 (\varepsilon_r, \varepsilon_{adm}) \int_{a}^{b} \int_{a}^{b} \int_{0}^{\pi} \cos \varphi \frac{\cos \varphi - k^2 r}{r} + i k \cos \varphi - i \frac{k^3 r^2}{6} \cos \varphi d \varphi d \rho d \rho'$$

$r = \sqrt{\rho^2 + \rho'^2 - 2 \rho \rho' \cos \varphi}$ the distance between the source point and the field point, $\rho'$ and $\rho$ are respectively the radial coordinates of these points at the aperture of coaxial probe. Using inverse problem approach, it is possible to determine the complex permittivity of the MUT, resolving a global optimization problem. Minimization problem is solving with Particle Swarm Optimization (PSO) [10].

A Sensitivity Analysis (SA) was realized to define which parameter of the reflection coefficient model related to the normalized probe admittance model by (2) was predominant [11]. SA has been based on the use of reduced sensitivity functions. Sensitivity functions are defined as the absolute variation of a simulation output $S^*$ induced by an absolute variation of the input parameters considered. In order to compare these coefficients with each other’s, the reduced sensitivity functions of $S^*$ versus parameter are defined. The sensitivity study has been performed for the input factors of (2), the real and imaginary part of the permittivity that are unknown and the coaxial probe inner (a) and outer (b) sizes that are a priori known with given uncertainties fixed to 2%. Outputs tested in SA were real, imaginary, modulus and phase (theta) of reflection coefficient. All reduced sensitivity functions are plotted on figure 4, for frequencies from 0.1 to 10 GHz.
By using the phase (theta) or the imaginary part of the reflection coefficient, the real part of permittivity should be easier identify in the range of frequencies between 0.5 to 6 GHz and the imaginary part between 2 to 10 GHz. By using the modulus or the real part of the reflection coefficient the imaginary part of permittivity could be identify between 0.5 to 1.5 GHz and the real part between by 2 to 10 GHz. Between 0.1 and 0.4 the variations on the imaginary part of permittivity have no effect on the reflection. As a consequence, it is not possible to identify this parameter between 0.1 and 0.5 GHz with this coaxial line. It must be emphasis that a carefully attention must be paid on the size of the coaxial probe since it is highly correlated to the permittivity in the range of frequencies between 0.1 and 1 GHz where the reflection is less sensitive to the permittivity. The sensibility analysis with reduced sensitivity functions has shown the ability to easily identify both imaginary and real of the permittivity by selecting the output as a function of the frequency. The fitness function given by equation 3 has been written as a function of frequency and input parameter that have to be identified.

$$\text{FF} = \left(\frac{\text{Re} \left(S^{*}_{11,\text{adm}}\right) - \text{Re} \left(S^{*}_{11,c,MUT}\right)}{\text{Re} \left(S^{*}_{11,c,MUT}\right)}\right)^2 + \left(\frac{\text{Im} \left(S^{*}_{11,\text{adm}}\right) - \text{Im} \left(S^{*}_{11,c,MUT}\right)}{\text{Im} \left(S^{*}_{11,c,MUT}\right)}\right)^2$$

(3)

The approach is validated on ethanol and then used on pork skin tissues at 23°C (figure 5).

4. 3D Thermal modelling of temperature distribution
This section presents the 3D numerical model developed and programmed in C-language. The thermal and electrical tissues properties are obtained from the developed benches on ex vivo animal tissues expected the blood perfusion obtained from [12].

4.1. Finite element formulation
Induced electromagnetic and thermal quantities are computed on tetrahedral meshes conforming to real human organs. Tetrahedral meshed are assembled from medical imaging Computerized Tomography (CT) scans or MRI sequences with the Amira commercial software (figure 6 to 9). For electromagnetic calculation, the vector wave equation is written in terms of total electric field, from the Maxwell equations. The time-harmonic FE formulation is obtained by applying the Galerkin weighted residual method. In order to take into account the wave propagation out of the FE domain, the FE formulation is coupled with a first order vector Engquist Majda absorbing boundary condition. The discretization is obtained by using the incomplete first order edge elements. An iterative method conjugate gradient type solver with a potential projection preconditioning technique is used to solve the matrix system [13]. The relevant quantity for hyperthermia treatment is not the E field itself but rather the electromagnetic energy absorption rate in tissue also called Specific Absorption Rate (SAR).
The heat transfer in living tissues is a complex process involving multiple phenomenological mechanisms. Among all the models proposed to analyse the heat transfer and to compute the thermal elevation in biological tissues, Penne’s bio-heat equation [14] is the most commonly used due to its simplicity and its validity. It handles the intuitive concept of blood perfusion which represents the blood flow rate per unit tissue volume. It includes microcirculation due to both capillaries network, small arterioles and venules of diameter lower than 100 µm. In the case of tissue submitted to electromagnetic wave, the resulting Pennes bio-heat equation is given by equation (3).

\[ \rho_t C_t \frac{\partial T}{\partial t} = \nabla (k_t \nabla T) - C_b \omega_b (T - T_a) + Q_{em} + Q_m \]  

(3)

with \( Q_m \) the energy generated by the metabolic process, \( T_a \) the temperature of arterial blood assumed constant at 37 °C, \( C_b \) the specific heat of blood, \( \omega_b \) the blood perfusion (kg.m\(^{-3}\).s\(^{-1}\)), \( C_t \) the specific heat of tissues, \( k_t \) the thermal conductivity, \( \rho_t \) the mass density and \( Q_{em} \) the electromagnetic power deposition. \( Q_{em} \) is linked to the SAR computed by the electromagnetic model (\( Q_{em} = \rho \text{SAR} \)). The temperature elevation induced by the interstitial hyperthermia is limited to a small volume with low vascularization, so the blood perfusion has been considered as a constant; its variation with the temperature is not considered.

The 3D FE numerical model developed is used to determine the temperature distribution in the case of a clinical treatment of cancerous tumour with the interstitial hyperthermia prototype probe. This modelling leads to a FE mesh made of 39 052 nodes, 213 755 tetrahedral elements and 259 648 edges. The figures 11 and 12 show the numerical results obtained with the developed 3D numerical FE model, the results are presented in term of temperature distribution, on a sagittal and a coronal view inside the patient. The figure 10 presents the tetrahedral patient model and the boundary conditions.
4.2. Experimental results

The phantom is contained in a rectangular Plexiglass box (length 200mm, depth 150mm, height 100mm) and the interstitial prototype probe is inserted in its center. The figure 13 represents the local evolution of temperature in the phantom, close to antenna (less than 1mm). The local temperature is measured with a fiber optic thermometer (Luxtron One).

![Figure 13. Local temperature evolution in the phantom near the metal tip antenna.](image)

The figures 14 and 15 show respectively the temperature distribution on a face of the phantom for two different moments, at t=120 s and t=240 s. The interstitial antenna is positioned at 10 mm depth of this measured face. The surface temperature is obtained with an infrared camera.

![Figure 14. Surface temperature distribution on the phantom at t=120s.](image) ![Figure 15. Surface temperature distribution on the phantom at t=240s.](image)

5. Conclusions and perspectives

A global procedure design for interstitial hyperthermia ablation devices has been developed and exposed. All the tools used in the design procedure are developed locally and implemented in C-language, except for the mesh procedure that used a commercial software. An experimental test bench including prototype interstitial probe, phantom, microwave source, amplifier generator and thermal measurement devices has been developed. For this first study, the hyperthermia device is based on a simple monopole metal-tip antenna operating at 915 MHz. The perspectives of these works are oriented along six axes. First, different phantoms with equivalent electric properties of tissues and used the procedure on ex vivo animal tissues (for example on bovine liver) will be developed. Second, the electric fields and temperature measurements realized on phantom and on ex-vivo tissues will be compared to numerical results obtained from the 3D numerical simulations. Third, the shape and the dimensions of the antenna prototype probe will be optimized with genetic algorithm or particle swarm optimization methods, to obtain the best possible temperature distribution in the target area. Then, the
volume of the necrosis induced by the microwave field will be evaluated numerically and measured. Complex microwave ablation devices adapted for specific medical treatment will be developed, and the possibility to modify the tissues properties by injected liquid in the target area will be studied, to increase the electromagnetic field concentration on the tumour. The last step which is the most important will be the realization of the tests to obtain the certification for the used in clinical routine.

A platform has been developed to determine the thermal tissues properties. The uncertainties due to each method used have been quantified and also the influence of temperature on thermal tissues properties. The next steps are oriented to determination of thermal characteristics of several others ex vivo animal tissues. The influence of the time between the sacrifice and the realization of the measure will be analysed. The verification of bone isotropy may be also studied.

Concerning the determination of the electrical tissues properties, several perspectives of this work are considering. Firstly, a comparison in term of efficiency and robustness for the identification of tissue permittivity between the Levenberg Marquardt and the PSO algorithm will be done. Secondly, the mono-layer approach presented in this paper will be enhanced for applications on bi-layered or multi-layered MUT and thirdly a micro coaxial probe will be developed. In order to investigate a larger frequencies range, a coaxial probe with different sizes will be tested. The variation of tissues properties with temperature will also be studied.

References

[1] Ryan TP, Turner PF and Hamilton B 2010 Interstitial microwave transition from hyperthermia to ablation: historical perspectives and current trends in thermal therapy *Int J Hyperthermia*. 26(5) 415

[2] Chou CK 2007 Thirty-five years in bioelectromagnetics research *Bioelectromagnetics* 28 3

[3] Shi W, Liang P, Zhu Q, Yu X, Shao Q, Lu T, Wang Y and Dong B 2011 Microwave ablation: results with double 915 MHz antennae in ex vivo bovine livers *Eur J Radiology* 79 214

[4] Simon CJ, Dupuy DE and Mayo-smith WW 2005 Microwave ablation: principles and applications *Radiographics* 25(Suppl. 1) 69

[5] Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, and Schlag PM 2002 Hyperthermia in combined treatment of cancer *The Lancet Oncology* 3

[6] Greef M, Kok HP, Correia D, Borsboom PP, Bel A and Crezee J 2011 Uncertainty in hyperthermia treatment planning: the need for robust system design *Physics in Medicine and Biology* 56(11) 323

[7] Kakehi M, Ueda K, Mukojima T, Hiraoka M, Seto O, Akanuma A, et al. 1990 Multi-institutional clinical studies on hyperthermia combined with radiotherapy or chemotherapy in advanced cancer of deep seated organs *Hyperthermia* 6 719

[8] Coquard R and Panel B 2009 Adaptation of the flash method to the measurement of the thermal conductivity of liquids or pasty materials *Int J of Thermal Sciences* 48(4) 747

[9] Ritz E and Dressel M 2008 Analysis of broadband microwave conductivity and permittivity measurements of semiconducting materials *J. Appl. Phys.* 103(8)

[10] Marion R, Scorretti R, Siauve N, Raulet MA and Krähenbühl L 2008 Identification of Jiles-Atherton model parameters using Particule Swarm Optimization *IEEE Trans. on Magn.* 44(6) 894

[11] Kelton WD and Barton RR 2003 Experimental design for simulation *Proceedings of the 2003 winter simulation conference New Orleans USA* 59

[12] Kanai Y, Tsukamoto T, Saitoh Y, Miyakawa M and Kashiwa T 1997 Analysis of a hyperthermic treatment using a reentrant resonant cavity applicator for a heterogeneous model with blood flow *IEEE Trans. Magnetics* 33(2) 1661

[13] Siauve N, Nicolas L, Vollaire C, Nicolas A and Vasconcelos JA 2004 Optimization of 3D SAR distribution in local hyperthermia *IEEE Trans. on Magn.* 40(2) 1264

[14] Pennes HH 1948 Analysis of tissue and arterial blood temperatures in the resting human forearm *J. Physiol.* 93