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Preliminary Study of Bone Tumors Hyperthermia at Microwaves Using Magnetic Implants

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***Abstract*—Microwave hyperthermia as therapeutic modality in oncology can be the next breakthrough technology if translated properly to the clinical practice. For deep-seated tumors such as bone cancers, antennas and radiating sources fails in achieving therapeutic temperatures without overheating healthy tissues. In this framework, magnetic implant to be used as thermo-seeds exposed to a several kHz magnetic field were studied. So far, the possibility of using magneto-dielectric biocompatible implant for performing microwave hyperthermia was not studied. In this work, we propose a simplified mono-dimensional electromagnetic model to study the propagation in a multilayer structure by means of the wave-amplitude transmission method. The model is aimed at finding suitable properties of the bolus, to be used as matching medium, while determining a set of working frequency for performing an effective treatment using magnetic implants. Then, we investigate the temperature evolution to determine, preliminarily, the feasibility of this innovative treatment modality.**

***Index Terms*—hyperthermia, magnetic materials, microwaves, propagation.**

I. INTRODUCTION

Microwave (MW) hyperthermia treatment (HT) is an oncological thermal therapy which aims to increase the temperature of a target, malignant tissue in the range 41°-43°C, by exposing a given body site to electromagnetic (EM) radiation, and so enhancing the effectiveness of radio- and chemotherapy [1]. MW HT can be performed at different frequencies (~13 MHz, 413 MHz, 915 MHz and 2450 MHz), administering the EM signal by using electrodes, truncated waveguides, horn, patch or dipole antennas [2]. To perform a high-quality treatment an accurate treatment planning phase has to be carried out by performing numerical EM and thermal simulations, aimed at identifying the extrinsic antenna parameters (e.g., amplitudes and phases) to selectively heat a target tumor [3]. However, despite the aid of these engineering tools, some cancers and body sites are very difficult to treat with MW HT [1]-[3]. Among these problematic neoplasms, bone cancers are deep-seated tumors which would severely benefit from HT. Indeed, HT could open new clinical possibility for empowering the treatment of these radio- and chemoresistant tumors [4]. However, HT treatment in the MW regime is not trivial for these biological targets [1]-[4].

In this framework, alternative modalities for performing the HT of bone tumors were studied. In particular, given that the surgical resection of the tumor is unavoidable, and that bone tissue is damaged, an implant is needed for mechanical and orthopedic purposes [5], as shown in Fig. 1.

However, after the operation, residual cancers cells can still be present in the surgical bed, thus leading to high tumor recurrence rates (~40%) [4]. Therefore, if the implant material (e.g., a polymer or a ceramic) is loaded with magnetic nanoparticles, then, exposing it to a radiofrequency (RF, herein in the range 100-700 kHz) magnetic field, then heat is dissipated and transferred to the surrounding tumor cells, achieving hyperthermic conditions [5]. In this way, two therapeutics needs would be satisfied with a single device.

The feasibility of performing HT with magnetic implants at RF was demonstrated, but, in the open literature, the possibility of operating a faster, more homogeneous heating of magnetic implants and bone tumors under MW was not investigated yet. In this framework, it is mandatory to perform a preliminary study aimed at identifying the possible working bandwidths, and performing a simplified treatment planning by estimating the temperature increase to assess the feasibility.

In this work, we propose a mono-dimensional model for studying the propagation in a multi-layer structure mimicking a typical body site affected by bone tumors, with a recently characterized magneto-dielectric as implanted thermo-seed. Then, by using the wave-amplitude transmission matrix (WATM) method, the reflection and transmission in the structure are studied. The transient temperature elevations in the human tissues are studied.

II. MATERIALS AND METHODS

A. Material Selection for Magnetic Scaffold

Several requirements must be considered for selecting a suitable magnetic material for performing MW HT of bone tumors. As first, the implant material should be biocompatible and allow to be manufactured with rapid prototyping or

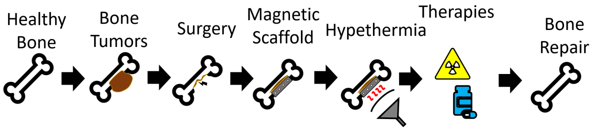

Fig. 1. Concept of Microwaves (MW) hyperthermia treatment (HT) of bone tumors with magnetic scaffolds.

additive manufacturing methods, such as fused deposition modeling. Furthermore, from the therapy, and the electromagnetic engineering point of view, the magnetic implant has to be a lossy, dispersive medium, presenting dielectric and magnetic losses capable of achieving temperature increase of about 3-7°C in the surroundings [5]. In this framework, the commercially available magnetic poly-lactic acid (PLA) from ProtoPasta is an appealing candidate. Recently, this off-the-shelf material was characterized by a dedicated broadband microwave magneto-dielectric spectroscopy technique [6], in the range 0.1-8 GHz.

B. 1D Propagation Model and Selection of Working Frequencies

Bone tumors can affect several body sites, mainly limbs and spine [4]. The geometry is simplified and assumed to be a planar, multilayered structure composed of $N = 6$ layers, shown in Fig. 2. The layers of biological tissues are skin, fat, muscle, a generic bone tumor. Two semi-infinite media are considered, i.e., the bolus/matching medium, having a relative permittivity ranging from ϵ_0 to 80, and the magnetic implant. The role of the bolus is to avoid skin overheating [4]. The thicknesses and physical sizes of the tissue layers are derived from [5] and reported in Tab. 1.

The system is assumed to be homogeneous and indefinite in the xy-plane. A planar, linearly polarized, time-harmonic transverse-magnetic (TM) wave is impinging on the system shown in Fig. 2, traveling along the z-direction. The media are characterized by a complex permittivity ϵ_n, an electrical conductivity σ_n (S/m) and permeability μ_n, for $n = 1, 2, \ldots, N$.

The EM properties of the biological tissues are taken from [7], whilst the microwave response of bone tumors is derived from the data found in [5]. All tissues are assumed to be non-magnetic, so that $\mu_n = \mu_0$. As regards the magnetic implant, we used the experimental data from [6].

The system shown in Fig. 2 is analyzed by using the wave-amplitude transmission matrix (WATM) method [8]. By knowing the amplitude of the propagating and reflected electric field, along the x-axis, E^1_{x+} at the first layer, the multilayered structure can be fully described by

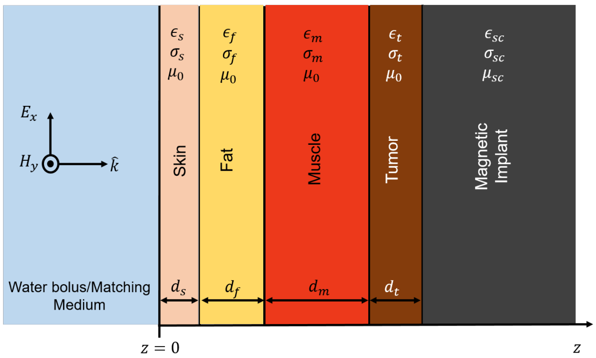

Fig. 2. Simplified geometry of the problem: A TM plane wave impinging on a multilayer structure composed of skin, fat, muscle, tumor tissue and a magnetic implant, assumed as semi-infinite medium.

TABLE I. PHYSICAL DIMENSION OF THE 1D PHANTOM

	Thickness (mm)	Variable name
Skin	1.5	d_s
Fat	10	d_f
Muscle	45	d_m
Tumor	10	d_t

$$\begin{bmatrix} E^{(1)}_{x+} \\ E^{(1)}_{x-} \end{bmatrix} = [M_1][T_1][M_2][T_2] \ldots [T_{N-1}][M_{N-1}] \begin{bmatrix} E^{(N)}_{x+} \\ 0 \end{bmatrix} \quad (1)$$

The matrix M_n account for the EM wave in the n-th medium as a function of the MW signal in the $n+1$ medium, so that

$$M_n = \frac{Z_n - Z_{n+1}}{Z_n + Z_{n-1}} \begin{bmatrix} 1 & \frac{2Z_n}{Z_n + Z_{n+1}} \\ \frac{2Z_n}{Z_n + Z_{n+1}} & 1 \end{bmatrix} \quad (2)$$

where the wave impedance for the n-th medium is

$$Z_n = \sqrt{\frac{\mu_n}{\epsilon_n}} \quad (3)$$

The propagation in the n-th layer is described by the matrix T_n, defined as

$$T_n = \begin{bmatrix} e^{k_n d_n} & 0 \\ 0 & e^{-k_n d_n} \end{bmatrix} \quad (4)$$

being $k_n = j\omega\sqrt{\mu_0 \mu_n \epsilon_0 \epsilon_n}$ the wavenumber in the n-th medium.

By relying on the electric field continuity at the interface between n-th and $n+1$-th layers, and that the field amplitude can be computed considering the forward and backward propagating waves, the system

$$\begin{bmatrix} E^{(1)}_{x+} \\ E^{(1)}_{x-} \end{bmatrix} = \begin{bmatrix} \xi & \zeta \\ \gamma & \delta \end{bmatrix} \begin{bmatrix} E^{(N)}_{x+} \\ 0 \end{bmatrix} \quad (5)$$

From Eq. (5), the total reflection (ρ_t) and transmission (τ_t) coefficients can be found as

$$\rho_t = \frac{\gamma}{\xi} \qquad \tau_t = \frac{1}{\xi} \quad (6)$$

Therefore, the reflection (R) and transmission (T) can be found

$$R = |\rho_t|^2 \qquad T = \frac{\sqrt{\epsilon_n \mu_n}\cos\theta_1}{\sqrt{\epsilon_1 \mu_1}\cos\theta_n}|\tau_t|^2 \tag{7}$$

The WATM method is implemented in Matlab (The MathWorks Inc., Boston, USA). The reflection and transmission is studied in the frequency range from 0.1-8 GHz to find suitable matching medium/bolus properties and to determine the operative bandwidth to perform the MW HT on bone tumors in an effective way.

Then, the total power per volume unit $Q_{EM}(z)$ (Wm^{-3}) is quantified and the specific absorption rate (SAR) is evaluated as [4]

$$SAR = \frac{Q_{EM}(z)}{\rho} \tag{8}$$

where ρ is the tissue density in kg·m^{-3}.

C. *Hyperthermia Treatment*

The system is assumed to be exposed to the impinging linearly polarized uniform plane wave, with a peak power density of 10 Wm^{-2}, for a limited duration. Therefore, a first heating stage, during which the electromagnetic power deposit according to dielectric heating, induced frequencies and magnetic losses due to hysteresis losses, occurs. When the external MW stimulus is switched-off, the biological system cools by heat diffusion. The minimum duration of typical hyperthermia treatment time is about 60 min [1]-[4]. In this framework, the time constant of the EM problem is much lower than the duration, thus allowing to disregard transient effects and to decouple the thermal problem.

The Pennes' bio-heat transfer (PBHT) equation was solved [4], [5], [9]

$$k\frac{\partial^2 T}{\partial z^2} + h_b(T_b - T) + Q_{met} + Q_{EM}(z) = C\rho\frac{\partial T}{\partial t} \tag{9}$$

where $T = T(z)$ is the temperature (°C) and T_b is the arterial blood temperature of 37°C, t is time (min), k is the thermal conductivity (Wm^{-2}K^{-1}), C is the specific heat capacity (Jkg^{-1}K^{-1}). The term Q_{met} is the metabolic heat (Wm^{-3}). The effect of blood perfusion is included in the term $h_b = \rho_b C_b \omega_b$, i.e. the product of blood density (ρ_b) and specific heat C_b, and the perfusion rate of a tissue (ω_b, s^{-1}).

Eq. (9) is solved assuming that the $T \rightarrow T_b$ for $z \rightarrow \infty$, and considering continuity of temperature and heat fluxes at the interface between different media. At the skin-bolus interface we simulate the flow of the liquid bolus [4] as an effective convection mechanism, so that a Robin condition applies [4], [5]

$$k\left.\frac{\partial T}{\partial z}\right|_{z=0} = h_c[T - T_{bolus}] \tag{10}$$

where h_c is the heat transfer coefficient, assumed to be equal to 150 Wm^{-2}K^{-1}, and T_{bolus} was set to 20°C, given the deep seated target tumor [4].

TABLE II. THERMAL PROPERTIES OF TISSUES AND MAGNETO-DIELECTRIC AT 37°C

	ρ (g m^{-3})	k (Wm^{-2}K^{-1})	C (Jg^{-1}K^{-1})	Q_{met} (Wm^{-3})	ω_b (s^{-1})
Skin	1.05	0.37	3.40	1617	$1.73\cdot10^{-3}$
Fat	0.9	0.21	2.35	464.40	$1.50\cdot10^{-3}$
Muscle	1.09	0.49	3.42	910.10	$1.82\cdot10^{-3}$
Tumor	1.90	0.32	1.31	57000	0.5
Iron PLA	0.95	0.29	1.24	-	0
Blood	1.05	0.5	3.61	-	-

The PBHT equation was solved by assuming homogeneous, temperature-independent thermal properties for the biological tissues and implant material, reported in Tab. 1. The properties of skin, fat, muscle and tumors are taken from [5]. The thermal characteristics of the magneto-dielectric are taken from [10]. The problem was solved in Matlab.

III. RESULTS

The simplified exposure scenario of hyperthermia treatment of bone tumors using magnetic implant and performed at microwave frequencies (0.1-8 GHz) was investigated. By carefully investigating the magnetic implant it is possible to notice that the permeability of the implant is higher than unity and that the magnetic losses of the implant could be relevant, as shown in Fig. 4. As regards the dielectric properties of the system shown in Fig. 2, from Fig. 5, it is possible to notice a large contrast between the magneto-dielectric implant and the tumor, but also between the tumor and the muscle layers. Therefore, it is likely that internal reflections could establish at some frequencies, thus lowering the transferred power and hampering the HT effectiveness.

In this work framework, considering the possibility to select and design the type of bolus to match the MW signal with body impedances [11], we investigated the signal transmission in the system for different values of the dielectric permittivity of the medium and over

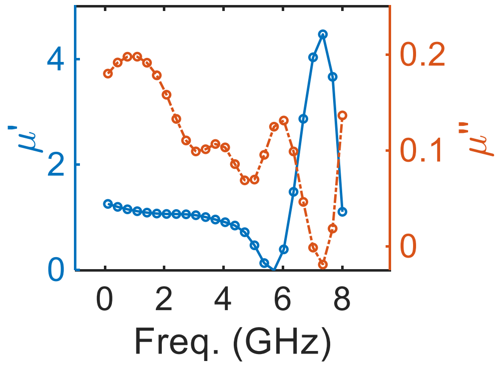

Fig. 3. Frequency variation fo the complex magnetic permeabilit, μ_{sc}, of the Iron ProtoPasta magneto-dielectric, biocompatible filemament, in real (μ') and imaginary part (μ'').

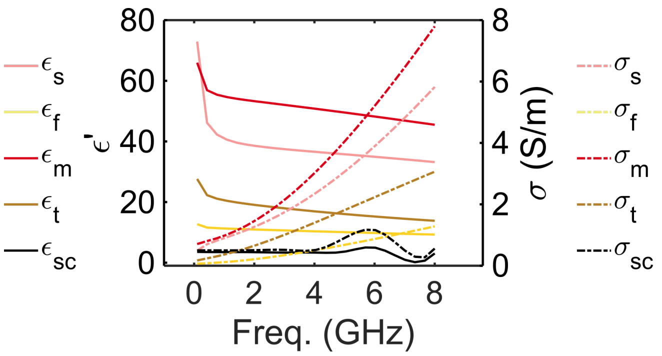

Fig. 4. Comparison of the dielectric permittivities (left axis) and electrical conductivities (right axis, in S/m) for the different tissues and the magneto-dielectric implant.

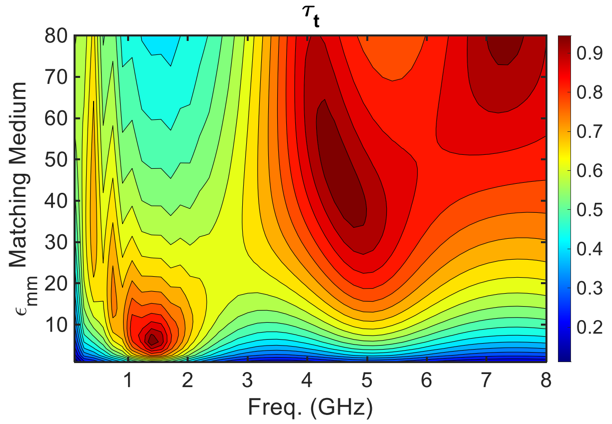

Fig. 5. Total transmission coefficient (τ_t) over frequency, as derived from the wave amplitude trasnfer matrix method for the simplified multilayer phatnom.

frequency, as usually done in the electromagnetic literature for this kind of problems [12]. The transmission map is reported in Fig. 5. It can ben noticed that for bolus permittivities around 5-30 it would be possible to operate between 0.915-1.5 GHz. Whilst, for watery bolus ($\epsilon_{mm} > 50$), the frequency range useful for converying EM energy inside tissues is from 4.25 to 8 GHz.

Despite the propagation study, the findings from Fig. 5 are not enough for planning the treatment. The power deposition and thermal aspects must be carefully taken into account [3]. Therefore, with our model, we investigated the SAR distribution in the main industrial, scientific and medical bands, as well as those promising identified from the analysis of Fig. 5. The SAR distribution is given in Fig. 6. It can be noticed that the levels in the skin are relatively high (~35-80 W/kg) for frequencies above 1.25 GHz. Whilst, the SAR peaks occurs at the fat-muscle interface for 434 MHz and 915 MHz. At the muscle-tumor interface, the transition is smooth, given the dielectric constant (Fig. 4). The presence of the magneto-dielectric implant, instead, results in a SAR value of 20 W/kg, for any values of frequency.

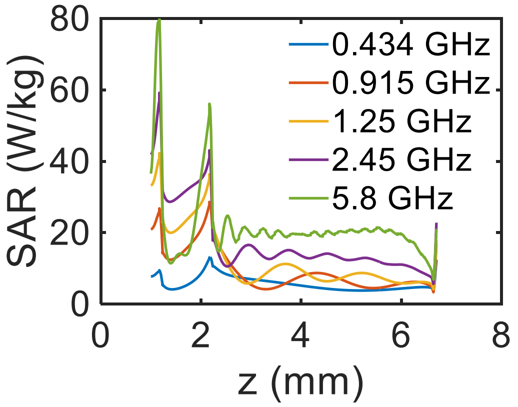

Fig. 6. Specific Absoption Rate (SAR), in W/kg, as a function of the z-coordinate, for different working frequencies.

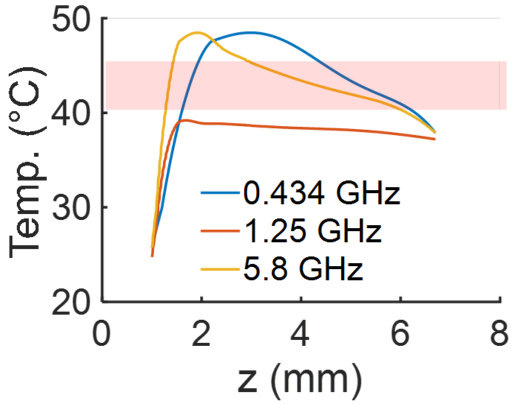

Fig. 7. Temperature evolution at t = 60 min along the depth (z-coordinate) for different working frequencies.

The temperature at final time for the multilayered phantom is reported in Fig. 7. It can be noticed that therapeutic temperatures ($T > 42°C$) can be achieved at 434 MHz and 5.8 GHz, but not at 1.25 GHz. At the lowest frequency of 434 MHz, there is a large and spread temperature peak, i.e. a hot spot, at the muscle location, which is coherent to the SAR distribution observed in Fig. 6. The high temperature in the muscle could be controlled with an external water bolus by controlling the temperature and water inflow, as found in the guidelines [13]. This is probably due to the lower transmission at 434 MHz (see Fig. 5). As the frequency increases, the heating is more homogenous and the target tumor region is heated effectively only in the case of $f = 5.8$ GHz. Therefore, from our numerical study, we demonstrated that there is room for performing bone tumor hyperthermia at MW by using magnetic biocompatible implants.

However despite this preliminary promising results, given that the community working in the field of microwave hyperthermia is working towards standardization by providing guidelines and recommendations, the best practices suggest that further theoretical and numerical work has to be done to study the MW treatment of bone tumors with magnetic implants [14], [15].

IV. CONCLUSIONS

In this work we preliminary analyzed the feasibility of using magnetic implants as thermo-seeds for performing bone tumors hyperthermia in the microwave range. We selected a commercial magnetic poly-lactic acid implant as candidates, since it was recently characterized in the range 0.1-6 GHz. We carried out our numerical investigations on simplified models of the electromagnetic propagation and of the thermal problem.

The proposed framework could be used as a platform for designing magneto-dielectric composite biomaterials with suitable properties at MW, or as a starting point for numerical studies aimed at designing a dedicated exposure apparatus for this innovative treatment modality. Next work must deal, relying on more accurate and realistic full-wave simulations, with parametric studies aimed at identifying suitable power density levels, or proposing focusing strategies, as well as different, time-modulated, forced-cooling approaches for delivering an effective and high quality hyperthermia treatment.

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