A Preliminary Propagation Study on Magnetic Scaffolds for Microwave Theranostics

Matteo B. Lodi

***Abstract*—Microwave hyperthermia is a promising therapeutic modality in oncology against deep-seated tumors such as bone cancers. However, antennas and radiating sources fails in providing the therapeutic heat without affecting the healthy tissues. Magnetic nanocomposite biomaterials, called magnetic scaffolds, can be implanted to be used as hyperthermia agents. The possibility of using magneto-dielectric biocompatible implant for performing microwave hyperthermia has been poorly investigated. Furthermore, the possibility of using magnetic scaffolds as microwave-responsive theranostic agents has never been explored. In other words, if and how the change of magnetic properties during the hyperthermia treatment could be detected by using microwave signal has been not investigated so far. In this work, a simplified mono-dimensional electromagnetic propagation model in a multilayer structure by means of the wave-amplitude transmission method has been proposed. The properties of the bolus-matching medium, a suitable set of working frequency for performing the hyperthermia treatment and the monitoring with microwaves has been found. The temperature increase in the tumor and scaffold have been simulated. Then, through the differential analysis of the variation of the transmission coefficient during the treatment it has been preliminarily determined that magnetic scaffolds could be used as microwave theranostic agents.**

I. Introduction

Cancer, the worldwide cause of death, demands for innovative and effective treatment solutions [1]. Despite their advantages, surgery radiotherapy and chemotherapy present several drawbacks [1], [2]. Hyperthermia treatment (HT) has been proposed as a new cancer therapy. HT is a treatment performed aiming at heating a targeted cancer volume. The goal is to increase the temperature above a given range, i.e., $T_t \in [40{,}44]$°C, for a time $t \geq 60$ min [1], [2]. In this condition, a cytotoxic environment (i.e., change in pH, oxidative stress, protein folding, etc.) establishes. HT has been proposed to be used in synergy with existing modalities and to empower them for the case of radio- or chemo-resistant cancers. Indeed, the effectiveness of radiotherapy and chemotherapy can be increased as follows. The hyperthermic temperature range enhance blood perfusion, the penetration of chemotherapeutics and the introduction of free radicals [1], [2].

HT can be performed in different ways and the therapeutic heat can be administered using several strategies. Recently, neoplastic pathologies (e.g., sarcoma) have been treated using electromagnetic (EM) energy. In particular, by exploiting the physical principle for which EM energy can be transformed and dissipated in heat, HT can be performed [1]. [2]. HT can be carried out by using microwave (MW) EM fields, and it can be performed at different frequencies (e.g., $f \sim 13, 413, 915, 2450$ MHz). The given body region to treat can be exposed to an EM signal by using electrodes, truncated waveguides, horn, patch or dipole antennas [3].

Despite being promising, MW HT has been found to be limited in treating deep-seated tumors, such as bone cancers. However, if applied to bone tumors, HT could open new clinical possibility for these radio- and chemo-resistant cancers [1]. Therefore, alternative modalities for performing the MW HT of bone tumors have to be found. Considering that the surgical resection is unavoidable, and given that bone tissue is damaged, a biomaterial implant for mechanical support and orthopedic needs is needed [4]. Furthermore, due to unclear surgical margin, residual cancers cells can lead to a ~40% tumor recurrence rate [5]. In this framework, a huge disruptive and innovative possibility is offered from nano-biomaterial science. In particular, if the implant material (e.g., a bio-polymer or a bio-ceramic) is loaded and functionalized with magnetic nanoparticles (MNPs), the implant is turned into a nanocomposite multi-functional and EM, MW-responsive biomaterial [6]. A magnetic nanocomposite biomaterial implant is called magnetic scaffold (MagS). These smart, theranostic and remotely-controllable magnetic biomaterials have been investigated for their multifunctional character in biomedical applications [6]. MagS can be synthesized by iron ion doping of bioceramics [4], [6] or by embedding MNPs in bio-polymers through physical manufacturing routes [6]. From a clinical perspective, these magnetic nanocomposites prosthetic implants can pave the route to a novel therapeutic modality in bone cancer treatment. In particular, after the surgical resection, it is supposed that a MagS is implanted and then EM energy is applied to cause the heat dissipation in the implant [7]. Then, the heat is transferred through conduction to the surrounding residual cancers cells and HT is achieved. So far, the treatment of bone tumors using MagS has been studied considering a radiofrequency (RF, herein $f \in [\sim 100{,}700]$ kHz) magnetic field [7], [8]. The feasibility of performing HT with MagS at RF has been demonstrated. However, the possibility of operating a fast, homogeneous heating of MagS and bone tumors under MW has been investigated preliminary in [9]. Therefore, the possibility of employing MW energy for performing the HT of bone tumors using MagS demands for further study. However, since HT is a

Matteo Bruno Lodi is with the Department of Electrical and Electronic Engineering, University of Cagliari, Cagliari 09012 IT (matteobrunolodi@ieee.org).

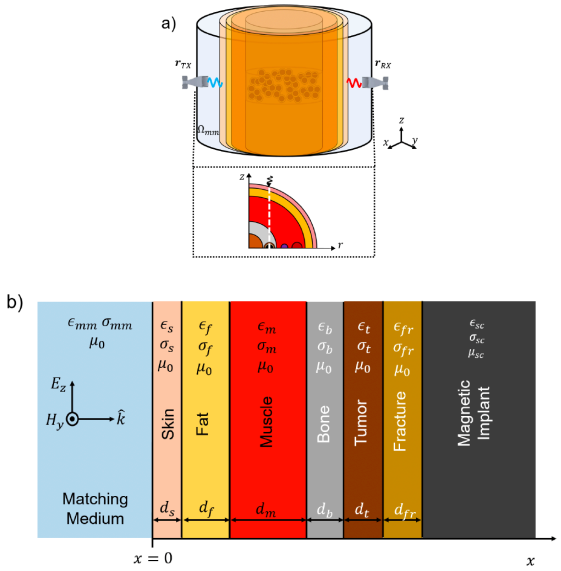

Figure 1. *a) Sketch of the proposed microwave (MW) system and scenario. b) Mono-dimensional layered model for a transverse magnetic (TM), linearly polarized plane wave impinging on a multilayer structure composed of skin, fat, muscle, tumor and fracture tissue and magnetic scaffold.*

standardized clinical procedure that has strict and demanding quality assurance guidelines [10], it calls for thermometry and monitoring strategies. Since the use of invasive thermometers is discourages, especially envisaging a non-invasive MW treatment, as sketched in Fig. 1a, different solutions have to be sought. The theranostic intrinsic nature of MagS has not been investigated so far. The possibility of using MW energy to contemporary heat the MagS and to sense temperature changes has been considered only very preliminary [11].

In this work, we propose a mono-dimensional model for studying the propagation in a multilayer biological structure in which a nanocomposite magneto-dielectric is implanted as thermo-seed and exposed to MW. By using the wave-amplitude transmission matrix (WATM) method, the reflection and transmission in the structure are studied for ensuring an effective heating and monitoring. The study is aimed at identifying the possible working bandwidths, and performing a simplified treatment planning. The bio-heat transfer problem has been solved to study the heating and the temperature changes in the tissues and MagS during the HT. Furthermore, to assess the theranostic potential of MagS, in this work the feasibility of using MW imaging for the monitoring of bone tumors with MagS is analyzed.

II. Materials

A. Magnetic Scaffolds

A suitable magnetic material for performing MW HT of bone tumors must be an implant material that is biocompatible and allow to be manufactured with rapid prototyping, while, from an EM engineering point of view, it has to be a lossy, dispersive medium, presenting dielectric and magnetic losses capable of achieving significant temperature increase ($\Delta T \in [3,7]$°C) in target tumor tissues. To satisfy these requirements, in the literature the possibility of embedding MNPs in bio-polymers of bio-ceramics

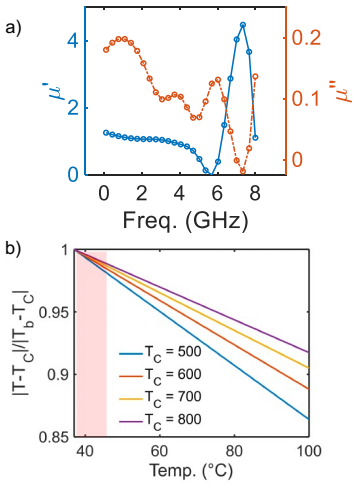

Figure 2. *a) Frequency variation fo the complex magnetic permeabilit, μ_{sc}, of the Iron ProtoPasta magneto-dielectric, biocompatible filemament, in real (μ') and imaginary part (μ'').*

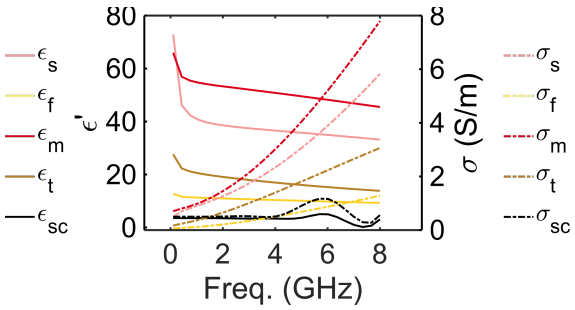

Figure 3. *Comparison of the dielectric permittivities (left axis) and electrical conductivities (right axis, in S/m) for the different tissues and the magneto-dielectric implant.*

through the nano-manufacturing of nanocomposite has been explored. However, a complete characterization of MagS at MW is not available in the literature, but a complete characterization of magneto-dielectric composite MW-absorbing materials can be found. In principle, some of them could be used for the HT of bone tumors. However, the biocompatibility and the feasibility of using these materials as MagS must be considered. We selected a composite ferromagnetic biomaterials characterized at MW that match the most relevant features of MagS as magneto-dielectric for performing as hyperthermia agents [7], [9]. The MagS EM properties are given in Fig. 2a and 3.

The modeling of the variation of MagS properties as a function of temperature is a relevant aspect. In this work, we assume that the temperature increase in the MagS is far from the Curie-Weiss temperature (T_c) of the material [11]. Hence, the material retains its natural ferromagnetic behaviour and the magnetic phase does not change. In this condition, relying on the classical mean-field theory of ferromagnets, the MagS magnetization is assumed to decreases as temperature increases, and the complex magnetic permeability is supposed to linearly decreasing, with the coefficient reported in Fig. 2b. On the other hand, the dielectric properties are assumed to be constant with the system temperature.

B. Biological Tissues

The dielectric permittivity and electrical conductivity of the skin, fat and muscle tissues (Fig. 1) at $T_b = 37$°C are provided in Fig. 3. As regards the properties of the fracture gap, they are assumed to be an average of blood and bone EM properties. On the other hand, the EM properties of the bone tumor it must be reported a lack of ex vivo or in vivo characterization. In this study we assumed the EM properties found in [9], [11].

III. Methods

In this section the formulation of the EM and thermal problem are provided. In this work the two problems are considered to be decoupled.

A. Electromagnetic Waves Propagation Model

Bone neoplasms can grow in different body sites (e.g., limbs, spine) [8]. In this work we consider a simplified planar geometry. A homogeneous and indefinite (in the xy-plane) multilayered structure composed of $N = 6$ layers, shown in Fig. 1b, is assumed to be exposed to a MW field. The system shown in Fig. 1b is supposed to be exposed to a planar, linearly polarized, time-harmonic transverse-magnetic (TM) wave that is traveling along the z-direction. The biological tissues are skin, fat, muscle, and a generic bone cancer. A bolus/matching medium, having a relative permittivity $\epsilon_{mm} \in [1,80]$, and the magnetic implant are considered as semi-infinite media. From the HT point of view, the bolus has to avoid skin overheating [1], [2], [10], whilst it acts as matching medium for ensuring a good penetration and transmission of the MW power. The thicknesses and physical sizes are provided in Tab. 1 [11]. The media are characterized by a complex permittivity ϵ_n, an electrical conductivity σ_n (S/m) and permeability μ_n, which is $\mu_n = \mu_0$ for $n = 1, \dots, N-1$ and equal to μ_{sc} for $n = N$. These properties have been introduced previously.

In this work the MW propagation in this system (Fig. 1b) is analyzed by using the wave-amplitude transmission matrix (WATM) method [12]. By knowing the amplitude of the propagating and reflected electric field, along the z-axis, E_{x+}^1 at the first layer, the multilayered structure can be fully described. Indeed, with the knowledge that the electric field is continuous 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 EM propagation is given by the following system [11], [12]

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

Therefore, the reflection ($\Gamma = \left|\frac{\gamma}{\xi}\right|^2$) and transmission ($1 - |\Gamma|^2$) can be derived.

The WATM method is implemented in Matlab (The MathWorks Inc., Boston, USA). The MW propagation problem is studied for $f \in [0.1,10]$ 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.

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

B. Bio-Heat and Thermal Modelling for Hyperthermia Treatment Planning

The exposure of biological tissues and biomaterials embedding magnetic nanoparticles to a MW field cause heat dissipation due to different mechanisms (e.g., dielectric heating, induced currents, hysteresis, etc.). The total electromagnetic power per volume unit $Q_{EM}(z)$ (Wm^{-3}) can be computed from the solution of the propagation problem and the specific absorption rate (SAR) can be derived as [9], [13]

$$SAR = \frac{Q_{EM}(z)}{\rho} \quad (2)$$

where ρ is the tissue density (kg·m^{-3}). The MW power (peak power density 10 Wm^{-2}) is supposed to be applied for a limited time interval. Therefore, as first, the EM power deposit according to dielectric and magnetic losses. As the external MW stimulus is switched-off, the biological system cools by heat diffusion. The minimum duration of typical HT time is ~ 60 min [1], [2], [8], [10]. Hence, the time constant of the EM problem is much lower than the duration. Therefore, transient effects can be disregarded, and the thermal problem can be decoupled. In this framework, to study $T(z,t)$, the following form of Pennes' bio-heat transfer (PBHT) equation has been solved [8], [13]

$$k\frac{\partial^2 T}{\partial z^2} + h_b(T_b - T(z)) + Q_{met}(z) + Q_{EM}(z) - C(z)\rho(z)\frac{\partial T}{\partial t} = 0 \quad (3)$$

where $T = T(z)$ is temperature (°C), $T_b = 37$°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 of a tissue (Wm^{-3}). Blood perfusion effects are represented by the term $h_b = \rho_b C_b \omega_b$, where the product of blood density (ρ_b), blood specific heat C_b, and the perfusion rate of a tissue (ω_b, s^{-1}) are computed. The PBHT has been solved assuming $T \to T_b$ as $z \to \infty$, while considering continuity of T and heat fluxes at the interface between different media. At the skin-bolus interface we simulate the flow of the liquid bolus [10] as an effective convection mechanism. The heat transfer coefficient, h_c, is assumed to be equal to 150 Wm^{-2}K^{-1}, and $T_{bolus} = 20$°C [10].

TABLE II. THERMAL PROPERTIES OF TISSUES AND MAGNETO-DIELECTRIC NANOCOMPOSITE IMPLANT 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	1.0	0.3	3.4	1617	$1.7\cdot10^{-3}$
Fat	0.9	0.2	2.3	464.40	$1.5\cdot10^{-3}$
Muscle	1.1	0.5	3.4	910.10	$1.8\cdot10^{-3}$
Tumor	1.9	0.3	1.3	57000	0.5
MagS	0.9	0.3	1.2	-	0
Blood	1.0	0.5	3.6	-	-

The PBHT equation has been solved by assuming homogeneous, temperature-independent thermal properties for the biological tissues and implant material, reported in Tab. 2 []. The problem was solved using Matlab.

B. MW Monitoring of Hyperthermia Treatment

To study how IHT impact on MW propagation, we solved the thermal problem thanks to the PBHE formulation, following a simplified multiphysics model to compute the temperature distribution, $T(z,t)$, in each tissue layer and in the MagS. Then we compute the average value $T(t)$ and studied the time evolution. We used the simulated temperature values to compute, for each time step of the simulated HT, how the MagS and tissues EM properties vary during the treatment. Indeed, for MagS $\mu_{sc} = \mu_{sc}(T)$ and for the tissues a linear variation of the dielectric properties has been assumed as in []. Then, for each time step we solved the MW propagation problem to study if significant variation occurs. Starting with the knowledge of the transmission coefficient at $t = 0$ and ($T = T_b \; \forall \, z$), i.e., $\Gamma(t = 0, T_b)$, we set a reference condition for the MW propagation. So, we computed $\Gamma(t,T)$ and performed a differential analysis considering as figure of merit the difference in the transmission coefficients with respect to the initial time, i.e. $\Delta[1 - |\Gamma|^2] = [1 - |\Gamma(t = 0, T_b)|^2] - [1 - |\Gamma(t,T)|^2]$.

IV. RESULTS

To evaluate the feasibility of using MW to monitor the IHT of bone tumors using MagS, we performed a novel analysis based on a mono-dimensional propagation model for the geometry shown in Fig. 1b. We investigated the transmission coefficient over the frequency range 0.1-10 GHz by varying the dielectric properties of the matching medium (ϵ_{mm}), and considering a representative magneto-dielectric nanocomposite biocompatible MagS. The map of the transmission coefficient is given in Fig. 4. For the MagS under analysis, a region with high transmission coefficient ($1 - |\Gamma|^2 \simeq 0.8$) can be noticed at ~ 2.45 GHz and $\epsilon_{mm} \simeq 20$. Other maxima in the transmission can be achieved for $\epsilon_{mm} > 40$ and $f > 4$ GHz. For $\epsilon_{mm} = 40$, the MW heating and the variations of the transmission coefficient during a simulated IHT have been investigated.

Despite the MW propagation study, the treatment planning must be refined. The power deposition and thermal aspects must be investigated []. For future applications, the development of a MW system (i.e., antennas) has to be

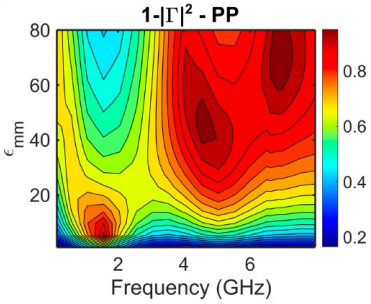

Figure 4. *Transmission coefficient as a function of frequency (f) and the properties of the matching medium (ϵ_{mm}) for the nanocomposite magnetic biomaterial.*

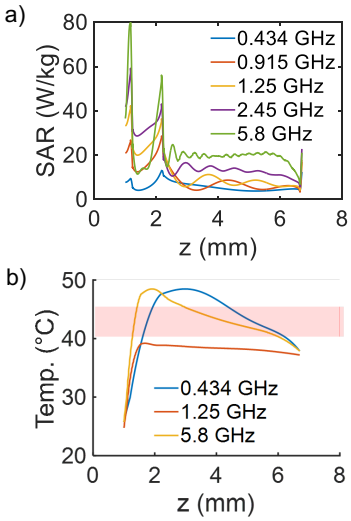

Figure 5. *a) Specific Absoption Rate (SAR), in W/kg, as a function of the z -coordinate, for different working frequencies. b)* Average temperature in the biological tissues at $t = 60$ min along the depth (z-coordinate) for different working frequencies.

envisaged (Fig. 1). Therefore, in this work we focus on industrial, scientific and medical (ISM) frequencies of 434 and 915 MHz, 2.45 and 5.8 GHz. The SAR distribution in ISM bands is reported in Fig. 5a. From Fig. 5a, it is possible to notice that the highest values occur in the skin layer (~35-80 W/kg) for $f > 1.25$ GHz. SAR peaks are evident at the fat-muscle interface ($f = 434, 915$ MHz). On the other hand, at the muscle-tumor interface, a smooth transition occurs. The presence of the nanocomposite magneto-dielectric implant results in SAR values of ~ 20 W/kg, for all f.

The pattern of $T(z, t = 60 \text{ min})$ is provided in Fig. 5b. Therapeutic temperatures ($T > 42$°C) can be achieved for $f = 434$ MHz and $f = 5.8$ GHz, but not at 1.25 GHz. For $f = 434$ MHz, where a good MW signal transmission was noticed (Fig. 4), a temperature peak, representing a hot spot, at the muscle location, has been found. The overheating of healthy tissues could be prevented by acting on the bolus temperature or switching the MW power on and off []. As the frequency increases much over 1.25 GHz, the heating is more homogenous in the target tumor region. For $f = 5.8$ GHz the HT regime can be established. With the proposed numerical study, it has been demonstrated that MW energy

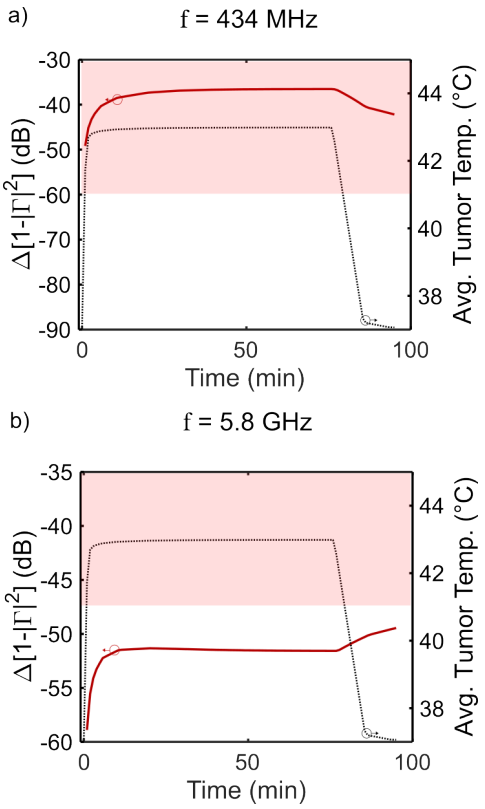

Figure 6. *Differential transmission coefficient, in dB, evaluated at the initial time t = 0 and during the treatment, for a)* $f = 434$ *MHz and* $f = 5.8$ *GHz. The black dashed line represent the average tumor temperature during the treatment.*

can be adopted to perform HT of bone tumors by using magnetic nanocomposite biomaterials as implant.

Despite these promising results, the goal of this work was to analyze if MW could be used, not only to heat the tumor target, but also to monitor in a non-invasive way the treatment and retrieve if the therapeutic threshold has been reached. Therefore, by using the solution of the PBHE, the modifications in the MW properties of MagS and tissues have been calculated and used to compute how the MW transmission varies during the HT.

The findings are provided in Fig. 6 for the two most relevant ISM bands identified in the EM-thermal study. At the lowest frequency of 434MHz (Fig. 6a) as the average tumor temperature $T_t(t)$ increases, the transmission coefficient increases of ~15 dB when the considered MagS is exposed to MW. As the MW field is turned off, blood perfusion cools down the biological tissues. In this case, the transmission coefficient tends to return to its initial value in ~1 min. For the highest ISM frequency ($f = 5.8$ GHz), a promising heating has been observed in Fig. 5b. However, as regards the modifications of the transmission coefficient during the HT are very low ($< -50\,dB$) and may not be measured in practice. The low change in the MW propagation may be due to the fact that the increased frequency result in a reduced penetration depth, which results in a lower mark of the EM properties change due to the MagS heating. Therefore, our preliminary but unique study has demonstrated the possibility to identify a working frequency for using MW to sense and monitor the temperature evolution of the hyperthermia treatment of bone tumors using magnetic nanocomposite biomaterials.

V. Conclusions

In this work we preliminary analyzed the feasibility of using magnetic nanocomposite biomaterial implants as theranostic agents for acting as thermo-seeds for performing bone tumors hyperthermia in the MW range and to behave as temperature-responsive agents for monitoring the therapy with microwaves. In this work a magneto-dielectric biomaterial implant functionalized with magnetic nanoparticles has been considered as case study. Numerical investigations on simplified models of the electromagnetic propagation and of the thermal problem have been performed to investigate if the HT could be performed and monitored using MW.

However, despite these preliminary promising results, further theoretical and numerical work has to be done to study how to use magnetic nanocomposite biomaterials as MW theranostic agents. The proposed framework could be used to design magneto-dielectric composite biomaterials with suitable properties at MW. On the other hand, the proposed models can be adopted as starting point for designing MW applicators and exposure apparatus for this innovative theranostic modality.

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