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A methodology for the measurement of the specific absorption rate of magnetic scaffolds

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***Abstract*—Deep-seated tumors can be treated performing local interstitial hyperthermia treatment (HT), using thermoseeds exposed to a radiofrequency magnetic field. Several novel biocompatible magnetic nanostructured thermo-seeds, defined magnetic scaffolds (MagS), are available to this aim. In the literature, the methodology adopted for the evaluation of the heating potential is lab specific, but also characterized by variable experimental conditions and different protocols. In this work, a perspective critical comment and analysis of the experimental protocols is provided. Then, a robust estimation methodology of the specific absorption rate (SAR) of MagS for the HT is provided, supported by numerical multiphysics simulations, an experimentally tested. The simulations highlight that overestimation in the SAR values can result from the sample misplacement. From the experimental analysis, it is found that the averaging of multiple temperature records is needed to reliably and effectively estimate the SAR of MagS for DST HT.**

Keywords—Hyperthermia, Magnetic Scaffolds, Radiofrequency Heating, Specific Absorption Rate

I. INTRODUCTION

Cancer is the main death cause worldwide. Deep-seated tumors are a class of neoplasms with significant incidence and mortality rates [1]. Examples are cervix, colorectal, bladder carcinomas, brain malignancies or bone tumors. Their treatment is challenging. Indeed, surgical operations are not always possible. Furthermore, often these tumors are radio- or chemo-resistant. Therefore, new treatment modalities are needed. To control the local recurrence and increase the survival rates for enhancing patients' life quality, hyperthermia treatment (HT) has been proposed as alternative, synergistic therapy. HT is a thermal therapy that aim to raise the temperature of a target tissue in the range [40,44]°C for a minimum of 60 min [2]. The temperature raise is known to provoke an immune system response, while altering the tumor microenvironment and leading to cytotoxicity [1], [2]. Furthermore, the increase in temperature augments the permeability to drugs and favors the creation of free radicals, thanks to the enhanced perfusion. Therefore, HT can synergistically enhance the effectiveness of existing interventional strategies, such as chemo- and radiotherapy [1].

The increase in temperature in a biological tissue can be determined by administering heat through the exposition of a body region to a given form of exogenous energy. EM energy can be used to perform HT. EM energy is noninvasive, contactless and highly controllable. Indeed EM-based HT to deep seated tumors has been achieved by using capacitive electrodes (8, 13.5 or 27.12 MHz) or by using arrays of antenna systems (433, 915 or 2450 MHz) [2]. However, for these particular cancers, these HT modalities result in a significant complexity in treatment planning and in a reduced treatment quality. Therefore, new way to perform HT against deep-seated tumors have been investigated.

For instance, colo-rectal cancers have been treated by implanting ferromagnetic bars and exposing them to a radiofrequency (RF) magnetic field to inductively heat the tumor volume. Furthermore, liver neoplasms have been treated by implanted stainless steel thermoseeds [1], [3]. The ferromagnetic metallic thermoseeds has the drawbacks of being not safe in magnetic resonance imaging (MRI) exams, while presenting biocompatibility and long-term stability issues [1], [3]. The heat is due to the eddy currents, requiring relatively high working frequencies $f \in [10,100]$ MHz. To avoid the use of metallic implant and lower the working frequencies, magnetic particle hyperthermia (MPH) for administering the HT at deep-seated tumor sites has been considered. However, problems in the administration, thermometry, potential toxicity and stability limited MPH against deep-seated tumors. Therefore, implants of biomaterials (bio-polymers or bio-ceramics) have been functionalized with magnetic particles (ferri-, ferro- or superparamagnetic) to manufactured a so-called magnetic scaffold (MS) to be used as thermoseeds to perform the HT of deep-seated tumors after their surgical resection [1], [3]. This magnetic graft is multifunctional and allows to perform the therapy while enabling the monitoring of the treatment, all based on EM fields. Furthermore, once that the neoplastic residual tissue is eliminated, the MS can be as biomedical device to home the healthy tissue. The research is ongoing in this field. For instance, recently, poly-caprolactone (PCL) scaffolds have been drop-casted using iron oxide nanocrystals to obtain MagS for bone tumor treatment [1].

To push the forefront towards new clinical landscapes, a more definitive takeoff of using MagS for the DST HT is required. To this end, it is fundamental that MagS must satisfy the minimum quality assurance requirements of the interstitial hyperthermia treatment. To treat a deep-seated tumor, a given MS must increase the system temperature to [40,44] °C, depositing a given amount of power per unit of mass (W/g) in the tumor volume in response to an RF field. Therefore, the quantification of MS hyperthermic potential is mandatory. In the literature, there is lack of a shared methodology for estimating the hyperthermic potential of MS. In this work, we aim at discussing the fact that the methodologies found in the literature are not suited for properly quantifying the HT efficiency of MS. Then, through a numerical study and experimental tests, as drafted in Fig. 1, we will highlight the factors that influences the measurements, and then provide an effective methodology for estimating the HT potential of MS.

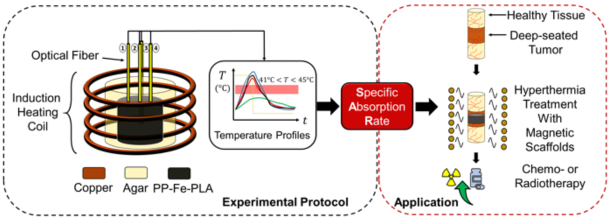

Fig. 1. Concept of the proposed methodology for the estimation of the specific absorption rate (SAR) of magnetic scaffolds (MS).

II. LITERATURE REVIEW

So far, the heating efficiency of MagS has been analyzed considering the temperature increase (ΔT) and time to reach it (Δt). From the perspective of EM engineering, in HT (especially in MPH), the physical quantity known as Specific Absorption Rate (SAR) is the standardized and common metric adopted to evaluate the efficiency of a system. SAR is a measure of the energy, per unit time, absorbed by the target volume surrounding a thermoseed. It must be not confused with specific loss power (SLP), even though these figures of merit have the same units (W/g). Indeed, SLP describes the power achievable per gram of magnetic element in the material and refers to the energy dissipated by the MNPs to the system. For MagS the adoption of SLP is not relevant, whilst the SAR as figure of merit is disregarded, or SAR has been evaluated with methodologically inappropriate means. Indeed, the comparison of HT performances of different MagS is challenging, depending on several factors. The HT tests are strongly dependent on the sample geometry and the measurement conditions (e.g., type of apparatus, field homogeneity, thermometry, etc.), but also on the estimation methodology. For instance, the influence of the geometry of a 3D-printed ferromagnetic MagS (i.e., pore size, distribution, porosity) on the HT performances has been poorly addressed and considered.

The HT potential of poly-metilmetacrilate (PMMA) scaffolds embedding Fe_3O_4 particles have been carried out in [3]. The sample has been put in saline and the temperature has been recorded with an infrared camera (IR). A variability of ± 4.3 °C from the average peak temperature has been reported. The repeatability issues are due to the MS sample placement inside the coil. In this case, the SAR has not been estimated. On the other hand, for a P_2O_5-Fe_2O_3-CaO-SiO_2 ferromagnetic glass ceramic scaffold for bone tumor HT a 0.26 W/g SAR value has been reported [3]. The MS has been tested in a saline environment. And exposed to a 0.5 mT magnetic field working at 100 kHz [3]. The temperature has been recorded every 60 s for 3 min with an optical fiber thermometer. For a MS embedding ferromagnetic $ZnFe_2O_4$, tested in 20 ml deionized water in a quartz cuvette, the estimated SAR varies in the range $5-9$ W per gram of sample [3]. The temperature rise has been recorded with a thermocouple for 3 min under the action of a 50 mT magnetic field working at 100 kHz. SAR values ranging from 5 to 30 W/g have been obtained for the weakly supeparamagnetic tri-calcium phosphate ($\beta - Ca_3(PO_4)_2$) co-substituted with Fe^{3+}-Co^{2+} ions thermo-seeds exposed to a 335 kHz and 13.5 mT magnetic field, in 1 mL of distilled water, for 40 min [3].

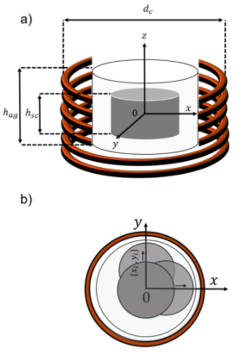

Fig. 2. a) System geometry for the numerical simulations of the different experimental setup for the calorimetric characterization of magnetic scaffolds (MagS). The heating system has conductors mad of copper, whilst the light grey cylinder represent the agarose matrix and the dark grey cylinder is the MagS. b) Representation of the possible misplacement of the scaffold in the agar phantom.

Noticeable differences are evident in the characterization of MS for HT. Very different working frequencies, field amplitudes and thermometric methods have been adopted. Also, the preferred media is deionized water, even though non-negligible convective contribution may influence the heat diffusion at the MS interface. Under these fuzzy, variable experimental conditions and setups, the scenario is concerning and deserves a critical and engineering approach. The estimation of the SAR of MS is at an early stage and must be tackled immediately in order to set the limits, regulations and validity criteria for quantifying the hyperthermic potential of these innovative medicine tools for the HT of deep-seated tumors.

III. MATERIALS & METHODS

A. Numerical Model

The finite element method (FEM) commercial software Comsol Multiphysics v5.5 (Comsol Inc., Burlinghton, MA USA) has been used to simulate the proposed experimental setup for the SAR measurements. The geometry for the simulation is shown in Fig. 2. A homogeneous cylindrical scaffold having magnetic permeability $\mu_r = 8$, dielectric permittivity $\epsilon_r = 2.5$ and elecrtical conductivity $\sigma = 10^{-6}$ S/m has been considered. The cylinder has diameter and height $d_{sc} = h_{sc} = 2$ cm. The thermoseed is placed in an agar phantom. The induction heating coil is a single layer coil having $N = 8$ turns. The coil is excited with a sinusoidal current (I_{exc}), working at $f = 400$ kHz, which is turn on at $t = 0$, and turned-off at specific time t_{off}. The calorimetric measurements are governed by the Ampere's law, in the time-harmonic fields formulation. The Magnetic Field interface from the AC/DC module has been used to study the electromagnetic problem. Once the magnetic field distribution has been computed, we evaluated the field homogeneity (ξ) in the MS volume by calculating the ratio between the mean value and the standard deviation of the magnetic field in the MS sample volume. The key aspect during SAR mesurements is the heat dissipation of MS. Depending on their magnetic features different mechanisms hold.

In this work, we will focus on a ferromagnetic MS. In detail a ferromagnetic poly-lactic acid (PLA) from ProtoPasta has been used [3]. The exposure of a ferromagnetic scaffold to a time-varying magnetic field determines a dissipated power (P_m in Wm^{-3}) to be computed from the experimental magnetization curve recorded using an Oxford Instruments 1.2H/CF/HT Vibrating Sample Magnetometer (VSM), at the system temperature of 300 K and by varying the magnetic field strengths in the range $[-1,1]$ T.

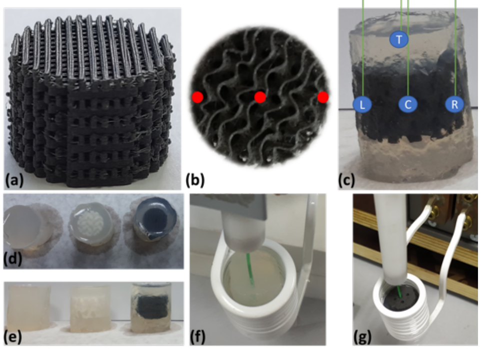

Fig. 3. a) System geometry for the numerical simulations of the different experimental setup for the calorimetric characterization of magnetic scaffolds (MagS). The heating system has conductors made of copper, whilst the light grey cylinder represent the agarose matrix and the dark grey cylinder is the MagS. b) Representation of the possible misplacement of the scaffold in the agar phantom.

Then, to investigate the heat transfer phenomena during the characterization of the heating efficiency of MS, a transient heat transfer equation has been solved. The physical properties of the samples are taken from []. The unsteady heat transfer equation is solved assuming continuity of temperature and heat flux. At the agar-air interface the heat exchange is ruled by convection. The system was considered to be in thermal equilibrium at $t = 0$ and a homogenous initial temperature distribution $T_a \; \forall \; x, y, z$ has been assumed. The Heat Transfer in Solid interface has been used.

B. *Experimental Tests and Proposed Protocol*

The geometry of the ferromagnetic MS samples has been created using Rhinoceros 7 (Mc Neel, Canada). Raise3D Pro2 Plus 3-D FDM (Fused Deposition Modeling) printer has been used with an extrusion temperature was 210°C, a 100% infill density and a 50 mm/s printing speed. The bed temperature was kept at 45°C. For the MS, three holes were opened from the top to the scaffold center, as shown with the red dots in Fig. 3b. The MS has been placed in a suitable agarose matrix (i.e., Figs. 2c-2g) to record the heat diffusion in four different positions (T - Top, L - Left, C - Center, and R - Right). Heating efficiency under magnetic hyperthermia conditions is evaluated through calorimetric measurements using the Easyheat AC field induction heating system, provided by Ambrell, operating at the power of 2.4 kW and at a frequency of 400 kHz. The applied magnetic flux density field intensity is 30 mT. The sample is deployed centered in the 8-turn induction heating coil with optical fiber placed in the corresponding positions.

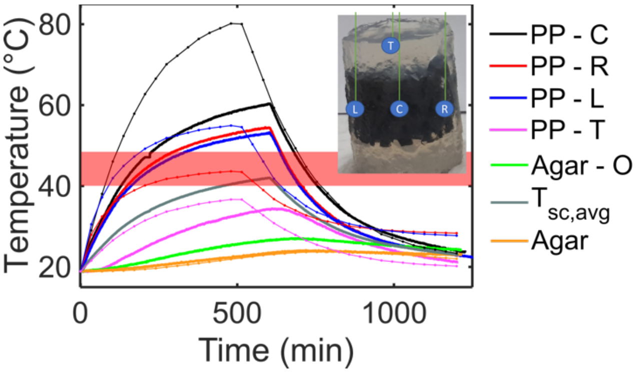

Fig. 4. Experimental temperature curves acquired in four different position (T = Top, C = Center, R = Right, L = Left) in the magnetic scaffold (MagS) and in the agarose phantom (O = Out). The simulated counterparts are reported in lighter colors. The shaded red area represents the typical temperature range for hyperthermia treatment.

IV. RESULTS

The HT potential of MS has been assessed through the experimental setup shown in Fig. 3 The different temperature curves recorded during the magnetic hyperthermia test are shown in Fig. 4. It can be noticed that the highest temperatures are reached in the MagS center (C - black curve), as confirmed by the simulations. By relying on the findings form our numerical study, using only the temperature curves acquired in points L and R would result in a misleading estimation of the SAR value. This is due to the fact that lower values of magnetic field strength and homogeneity are found at these locations. The different heat diffusion regime strongly affects the shape of the curve and can strongly impact on the final estimated SAR value. Indeed, if the temperature curve in the agar phantom is considered, an SAR of ~1 W/g is found for the MS considered in this study. On the other hand, if the temperature curves acquired inside the MS (i.e., C, R, L, T) are used to compute an average SAR. With this approach, a value of 1.2 ± 0.2 W/g is found.

V. CONCLUSIONS

This work deals with the investigation of the experimental parameters and estimation methodology on the SAR of MagS for the HT of deep-seated tumors. From our anlaysis, the factors affecting the SAR measurements are i) the AC magnetic field parameters, ii) the exposure system features, iii) the thermometric aspects, but also iv) the MagS properties (e.g., the type of magnetic particle, their volume fraction, aggregation degree), as well as the biomaterial geometry and architecture.

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