

Theoretical Considerations for the Design of Magnetic Scaffolds for Bone Tumor Hyperthermia

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Abstract

The effectiveness and the quality of the hyperthermia treatment of bone tumors using magnetic implants can be improved. To date, several biocompatible biomaterials loaded with magnetic nanoparticles have been manufactured and characterized. However, the intrinsic parameters of the so-called magnetic scaffolds are not tuned to perform an optimum hyperthermia treatment. This work, for the first time, deals with the theoretical modeling of bone tumor hyperthermia using magnetic scaffolds. The goal is to investigate the heating abilities of a synthetic, virtual set of potential implants. The analysis is oriented in identifying the most essential features and relevant parameters for providing unique, useful feedbacks, from an electromagnetic engineering point of view, to material scientists and clinicians.

1 Introduction

Hyperthermia (HT) is an established powerful clinical tool for enhancing the effectiveness of surgery, improve radio- and chemotherapy and controlling local recurrence of neoplastic cells [1].

Bone tumors are an invalidating and aggressive class of neoplasms, especially primary osteosarcomas [2]. Currently, as shown in Fig. 1, in presence of a bone tumor, surgery is performed to resect the pathologic bone [2]. However, tumor margins are not well defined, and the osteotomy can leave residual, radio-resistant cancer cells, leading to a 30% recurrence rate [2]. As additional drawback, the intervention creates a gap, which must be filled with an implant or a so-called scaffold. Given these limitations, new therapies were investigated [2]. HT of bone tumors was studied and tested. However, microwave hyperthermia with interstitial applicators resulted in poor effectiveness and severe drawbacks (e.g., increased number of surgical fractures).

As a result, to benefit all clinical advantages of HT, different way of administering and delivering the heat to bone tumors were investigated. An interesting solution from material science was suggested. By using magnetic nanoparticles (MNPs) and loading a biomaterial, a magneto-responsive prosthetic implant can be obtained [4]. If exposed to an alternating magnetic field, the MNPs dispersed in the biomaterials will act as localized heat sources for performing HT treatment [3, 4]. The HT can favor [1, 2]. given the presence of the prosthesis, the post-operative operations management can be facilitated. The concept is shown in Fig. 1. A MagS could favor to fight the cancerous cells, by enhancing radio- and chemotherapy, and then facilitate the repair process.

This type of HT modality is not new, since interstitial hyperthermia was already investigated and performed by inserting ferromagnetic steel implants as thermo-seed in deep seated tumors, such as colo-rectal cancers [5]. The main difference with MagS is that they are nanocomposite biomaterials, i.e., a bioceramic or biopolymer loaded or functionalized with MNPs, such as the iron-doped hardystonite bioceramic from [7]. However, in the literature, several MagS for bone tumor hyperthermia have been proposed [4]. These novel thermo-seeds present highly variable properties and are tested under very different conditions. The design of MagS is not driven by a set of quantitative and application-oriented rules. Indeed, the saturation magnetization of MagS can range from tens of kAm^{-1} to hundreds of kAm^{-1} [3, 4, 7]. This is due to different type of magnetism (e.g., ferri- and ferromagnetism, as well as superparamagnetism), but also on the widely spread amount of MNPs in the volume (from few % to 40-50%). As a result, the heating performances can be very different [3]: at 293 kHz and 15 mT, magnetic hydroxyapatite scaffolds can achieve a maximum temperature increase of 40°C in 1 min, whilst poly-caprolactone loaded with magnetite can reach 10°C in 5 min [4]. The heat dissipation, crucial for assessing the HT potential, is poorly investigated: the specific loss

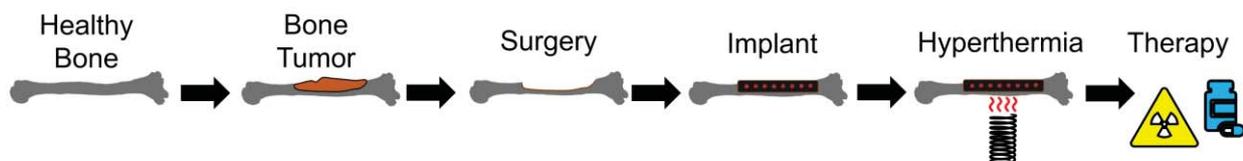


Figure 1. Narrative and schematic description of using implants as local heaters for performing hyperthermia treatment against bone tumor cells, after surgery, to improve radio- and chemotherapy effectiveness.

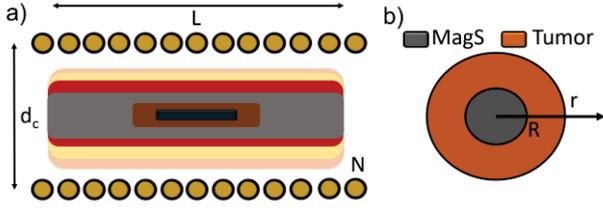


Figure 2. a) Illustration of the heating coil and the treatment setup. b) Simplified geometry of the problem. A magnetic scaffold (MagS) of radius $R=5$ mm is assumed to be implanted in a semi-infinite tumor medium.

power (SLP) sometimes is not measured and quantified [3, 4]. Furthermore, when performed, the experiments are carried out at a single frequency (around hundreds of kHz) and for a limited number of exposure configurations or field strengths (with an amplitude of few to tens of mT).

In this framework, the “best” magnetic scaffold and its properties could not be easily identified. Therefore, in this work, we propose to study from a theoretical point of view the hyperthermia treatment of bone tumors using magnetic scaffolds, in order to retrieve and highlight the most relevant implant characteristics and physical properties, in order to drive the design of these materials and to ensure a high-quality treatment [8].

2 Derivation of the Mathematical Model

2.1 State-of-the-Art

Interstitial HT with magnetic scaffolds could be understood and studied by relying on the theory of ferromagnetic implant heating from Stauffer et al. [5], or re-adapting the solutions to heat equation for magnetic fluid hyperthermia in steady [7] or transient form [9]. Finally, recently, a multiphysics, coupled non-linear model in a simplified 2D geometry of human limbs was proposed [4]. In this work, we want to study a steady-state condition in a simplified geometry, to highlight the most relevant parameters and properties of magnetic scaffolds for performing the hyperthermia treatment of bone tumors.

2.2 Geometry

We consider the case of a cylindrical magnetic scaffold, with radius R , implanted after the surgical excision of a bone tumor. The implant is considered surrounded by the residual tumor cells, which is assumed to be a semi-infinite medium, as shown in Fig. 2.

2.3 Model of Bone Tumor Hyperthermia with Magnetic Scaffolds

The alternating magnetic field (H) working at a given frequency f , is the cause of heat dissipation by the MNPs in the MagS. The exposure system can be a solenoid, a pancake coil, with N turns, length L and excited by a

current I , in which a human limb is inserted (Fig. 2(a)) [5]. To account for the electromagnetic field source in the problem, we can approximate our derivation by assuming the coil long enough, and by considering that if the coil diameter d_c is much larger than the scaffold diameter $2R$ (i.e., $d_c \ll 2R$), then a uniform and homogenous magnetic \vec{H} field in the geometry in Fig. 2 is present:

$$H \cong N \frac{I}{L} \quad (1)$$

Furthermore, the magnetic scaffolds are dielectric insulating objects, so that $\sigma \ll j\omega\epsilon$, being σ is the electrical conductivity (Sm^{-1}), $\omega = 2\pi f$ and ϵ is the dielectric permittivity of the medium. Hence, standard solution for conducting cylinder exposed to a plane wave could not be used in this case [5].

Relying on this simplification, the power dissipated by the magnetic scaffold (P , Wm^{-3}) can be quantified [4]. Being the field constant, the power dissipated by the MNPs in the implant can be written as [4]:

$$P_m = \pi f |H|^2 \chi'' \quad (2)$$

where χ'' is the imaginary part of the complex susceptibility of the magnetic scaffold, i.e., $\chi(f) = \chi' - j\chi''$.

In Eq. (2) is where the intrinsic material properties come into play. In fact, the complex magnetic susceptibility can be evaluated by using a Cole-Cole model [4]:

$$\chi(f) = \frac{\chi_0}{1 + (j2\pi f \tau_N)^{1-\gamma}} \quad (3)$$

where χ_0 is the equilibrium susceptibility, τ_N is the characteristic Néel relaxation time for the particle dipole moment and γ is the broadening parameter, set equal to 0.5. It was proven that the linear response theory and the Debye response do not apply when MNPs are constricted in a highly viscous or solid matrix, since the inter-particles interactions lead to a vanishing of the resonant response [4].

The equilibrium susceptibility can be calculated as:

$$\chi_0 = \frac{\phi_m M_s}{H} \left[\coth \left(\frac{\mu_0 M_s V_m H}{k_B T} \right) - \frac{k_B T}{\mu_0 M_s V_m H} \right] \quad (4)$$

where ϕ_m is the volume fraction of MNPs in the biomaterial, M_s is the scaffold saturation magnetization (Am^{-1}), V_m is the particle volume, μ_0 is the vacuum permeability (Hm^{-1}), k_B is the Boltzmann’ constant (JK^{-1}) and T is the system temperature. The relaxation time is defined as follows:

$$\tau = \tau_0 e^{\frac{K_a V_m}{k_B T}} \quad (4)$$

where τ_0 is a pre-exponential factor (ranging from ns to ps) and K_a is the anisotropy energy of the nanoparticle crystal (Jm^{-3}).

In Eq. (4) and (5) it is possible to immediately visualize which are the design parameters of magnetic scaffolds: ϕ_m , $M_s V_m$ and K_a . In fact, the amount of nanoparticles loaded in the biomaterial is a function of the manufacturing process, but it is a tunable quantity. The dipole moment of the MNPs and the crystal energy can be adjusted during particle synthesis, by controlling the dispersion of particle sizes and the coating of the MNPs.

After having underlined these crucial aspects, we can derive the imaginary part from Eq. (3):

$$\chi'' = \frac{1}{2} \chi_0 \frac{\cos\left(\frac{\gamma\pi}{2}\right)}{\cosh\left((1-\gamma)\ln(2\pi f\tau_N)\right) + \sin\left(\frac{\gamma\pi}{2}\right)} \quad (5)$$

Then, by substituting Eq. (5) in Eq. (2) we have found a closed-form equation for the power dissipated by a magnetic scaffold, exposed to a homogeneous magnetic field:

$$P_m = \frac{1}{2} \pi f |H|^2 \chi_0 \frac{\cos\left(\frac{\gamma\pi}{2}\right)}{\cosh\left((1-\gamma)\ln(2\pi f\tau_N)\right) + \sin\left(\frac{\gamma\pi}{2}\right)} \quad (6)$$

To evaluate the treatment outcome, we must solve the Pennes' Bioheat equation [4]:

$$\rho C_p \frac{\partial T}{\partial t} = k \nabla^2 T - \rho_b \omega_b C_b (T - T_b) + P_m \quad (7)$$

where ρ is tissue density, C_p is the specific heat capacity ($\text{J}\cdot\text{K}^{-1}\text{kg}^{-1}$), k is the thermal conductivity of the tumor ($0.32 \text{ W}\cdot\text{K}^{-1}\text{m}^{-1}$). The blood perfusion is included in the model and the terms with the sub-script "b" refers to blood thermal properties [1, 4, 5]. In particular $\rho_b=1050 \text{ kg}\cdot\text{m}^{-3}$ and $C_b=3617 \text{ J}\cdot\text{K}^{-1}\text{kg}^{-1}$. The tumor tissue perfusion ω_b is a limiting quantity and it is assumed be equal to 0.5 s^{-1} , for mimicking an osteosarcoma [4]. In Eq. (7), T_b is the blood arterial temperature of 37°C . Some assumptions are required to solve Eq. (7). Firstly, differently from [4], we consider the electromagnetic and thermal properties of the tissues to be independent from the temperature. Since we aim at evaluating the quality of hyperthermia treatment, the time scale is on the order of 30-60 min, thus implying that a steady state solution can be sought (i.e., $\partial T/\partial t \rightarrow 0$). Now, re-arranging, transforming the problem in spherical coordinates, neglecting the heat contact resistance at the interface of the two media, for $r > R$, by imposing that for $r \gg R$ holds that $T = T_b$ we can finally find the temperature increase as [5, 7]:

$$\Delta T = \frac{1}{3} \frac{R^3 P_m}{kr} \frac{e^{-\sqrt{\frac{\rho_b \omega_b C_b}{k}}(r-R)}}{1 + R \sqrt{\frac{\rho_b \omega_b C_b}{k}}} \quad (8)$$

Table I. Properties of MNPs for MagS

| MNPs | V_m (nm^3) | M_s (kAm^{-1}) | K_a (kJm^{-3}) |
|-------------------------|-------------------------|-----------------------------|-----------------------------|
| Fe_3O_4 | 44602 | 446 | 35 |
| FeCo | 7238 | 1800 | 1.5 |

By substituting Eq. (6) into Eq. (8), a theoretical formulation for investigating the influence and role of the magnetic material parameters on the proposed radiofrequency hyperthermia treatment of bone tumors is found.

3 Numerical Experiments

With the developed mathematical model, we want to study some virtual and potential magnetic scaffolds candidates for the treatment. We consider using 22 nm magnetite (Fe_3O_4) and 12 nm iron-cobalt (FeCo) nanoparticles for "manufacturing" our magnetic scaffolds. The properties are taken from [10] and reported in Tab. I. We assume to be able to load a biomaterial with a uniform population $\phi_m \in [0,50]\%$. By using Matlab 2019b (The MathWorks Inc., MA, USA) we investigate the power dissipation of two MagS. The dissipated power is studied as a function of field amplitude and of the working frequency. Then the final, steady temperature profiles in the bone tumor for the two MagS are simulated and compared.

4 Results

As magnetite-based scaffold and an iron-cobalt loaded one are considered as candidates for the hyperthermia treatment of bone tumors. The properties of the MNPs are rather different, as can be seen from Tab. I. Therefore, we investigated the frequency response of the imaginary part of the magnetic susceptibility [χ'' , Eq. (5)] and the magnetic power dissipated by the implant [P_m , Eq. (6)] for field amplitude between 0.1 Am^{-1} and 7 Am^{-1} , for working frequencies from 100 kHz to 700 kHz.

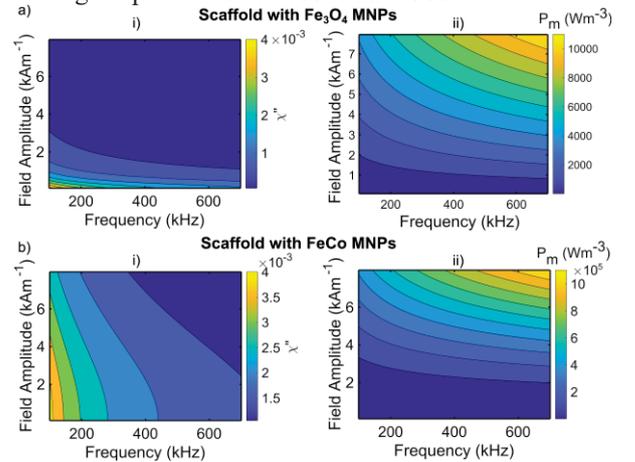


Figure 3. a) Scaffold with 0.5% of magnetite nanoparticles: i) imaginary part of magnetic susceptibility, ii) power dissipated per unit volume. b) Scaffold with 0.5% of iron-cobalt nanoparticles: i) imaginary part of magnetic susceptibility, ii) power dissipated per unit volume.

The results are shown in Fig. 3. The Fe_3O_4 MagS has a χ'' which is higher at fields below 2 kAm^{-1} and for frequencies below 200 kHz (Fig. 3(a).i). On the other hand, from our analysis, the FeCo MagS presents an enhanced χ'' up to 5 kAm^{-1} and 400 kHz. However, for both scaffolds, in terms of power, a more effective dissipation occurs for magnetic fields higher than 6 kAm^{-1} and frequencies of 600 kHz. Therefore, the temperature analysis is performed for these values.

The hyperthermic potential of the considered potential magnetic scaffolds against bone tumors can be evaluated by using Eq. (8). The ΔT patterns are shown in Fig. 4. As deduced from the previous analysis of the dissipated power, the FeCo MagS can rise the temperature above the therapeutic threshold of 42°C . The higher M_s of the FeCo MNPs cause P_m to be higher [χ'' , Eq. (5)], being ϕ_m the same for the two cases and the dependence from K_a is damped.

5 Conclusions and Discussions

This work dealt with the theoretical modeling of a novel form of interstitial and local hyperthermia treatment performed by heating, with a radio-frequency magnetic field, an implanted biomaterial loaded with magnetic nanoparticle. Through the derivation of an essential mathematical model, we investigated the heating abilities of magnetic scaffolds. With our theoretical analysis, we seized the most relevant features and properties (M_s , ϕ_m , K_a) for providing interesting feedbacks to material scientists and pave the route to new manufacturing strategies for magnetic scaffolds. The proposed model could be used to setup a simple, preliminary treatment planning and guidance platform.

The proposed mathematical framework could be expanded to better account for the electromagnetic aspects or to include more tissues (i.e., also the healthy, non-target ones). Future works must cope with the transient resolution of the heating equation [9] or a more in-depth modeling of the biological elements [1]. Finally, suitable optimization procedures and studies could be developed.

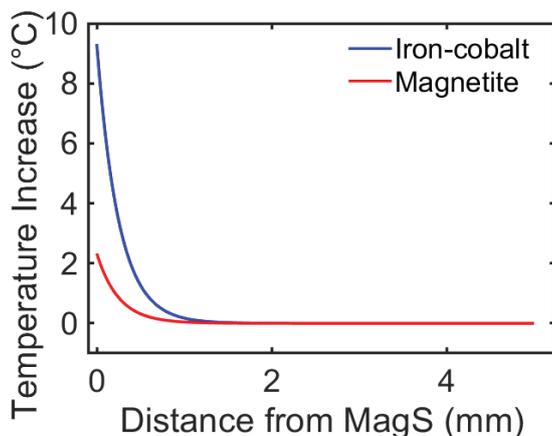


Figure 4. Steady-state temperature profiles for the two magnetic scaffolds investigated with the proposed theoretical model.

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