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Impact of different infusion rates on mass diffusion and treatment temperature field during magnetic hyperthermia

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ABSTRACT

In a magnetic hyperthermia treatment, malignant cells are ablated by the heat produced by power dissipation of magnetic nanoparticles (MNPs) under an alternating magnetic field. MNPs need to be placed inside the tumor region and a prominent method for doing this is to inject magnetic fluid directly into tumor. When this alternative is used, the efficiency of a magnetic hyperthermia treatment depends on factors such as the infusion rate and diffusion duration, since they affect the shape of MNP distribution inside tumor, which affects the temperature distribution during treatment. This paper analyzes the impact of different shapes of MNP distribution, caused by different infusion rates, on mass diffusion and treatment temperature field during magnetic hyperthermia. Three different shapes of MNP distribution were assumed based on images of experiments presented in literature, which used an agarose gel with different concentrations to represent different tissues. In addition, the distribution for a very low infusion rate, obtained from a model proposed in this paper, is used for comparison purposes. A proposed geometric model is used to numerically evaluate the impact of injection and diffusion parameters on a liver tumor considering the four different shapes of MNPs produced by different infusion rates. The simulation results demonstrate that the longer the diffusion duration and the larger the infusion rate are, the better the therapeutic effects are when a proper power dissipation of MNPs is used to control the maximum temperature reached during hyperthermia. To further improve the effective therapeutic area inside tumor, two alternative methods are also evaluated using the model proposed in this paper: multi-site injection and low Curie temperature MNPs. The results show that both of them can significantly improve the tumor area which is subjected to the therapeutic temperature, especially the latter one.

1. Introduction

Magnetic fluid hyperthermia has been considered one of the most important methods in the treatment of cancer due to its low invasiveness and side effects [1,2]. During therapy, when an external alternating magnetic field is applied, the magnetic nanoparticles (MNPs) injected into tumor region generate heat, which results in the ablation of malignant cells due to their sensitivity to high temperature values [2,3]. The ideal temperature field for magnetic hyperthermia is expected to be homogeneous and with values between 42 °C and 46 °C, since there is a higher probability of destroying tumor cells while not affecting the healthy ones if this temperature range is observed [4,5]. However, it is almost impossible to obtain an ideal temperature field in practice, even in the case that considers a homogenous distribution of MNPs inside the tumor area [6], uniform magnetic field [7], and optimization of MNP properties [8,9].

Although numerous works dealt with different aspects of magnetic hyperthermia setup to improve the effective treatment temperature field under a safety temperature [6–9], the injection strategy has not yet received enough attention. However, if the magnetic fluid is directly injected into tumor, the injection parameters play an important role in the treatment efficiency. The injection strategy involves the definition of the diameter of the needle used in the syringe, the infusion rate, and also the properties of the solution for injection and target to be injected. In a magnetic hyperthermia treatment, the properties of the target to be injected cannot be changed, since they are intrinsic to the patient. In addition, the properties of the solution for injection are usually defined before treatment, taking into consideration aspects as the desired heating mechanism and biocompatibility, so they cannot be

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modified freely. The needle is also supposed to have a relatively small diameter during clinical treatment in order to avoid unnecessary damage to the patient's body as well as to minimize backflow [10]. Once the needle diameter is defined, the infusion rate becomes the only main influencing factor for the effect of the injection strategy on MNP distribution inside tumor. However, few works in literature focus on the impact of infusion rate on mass transport and treatment temperature field during magnetic hyperthermia, mainly due to the complexity of the injection model and to the lack of *in vivo* experiments to confirm the theoretical results. The first work to present experimental results of MNP spatial distribution for different infusion rates was written by Salloum et al. [11] and uses an agarose gel with porous structures similar to human tissue for acquiring digital images of the nanofluid spreading. Based on that work, the effects of infusion rate and gel concentration on treatment temperature have been investigated using a simplified cylindrical simulation model in [12].

This paper extends the results of [12] by considering a more comprehensive simulation model, which incorporates the effects of particle aggregation in living tissues originally proposed in [13] and also considers the diffusion of MNPs after injection. Both improvements are important for clinical applications, since MNPs typically aggregate when inside living tissues and time for diffusion is a common practice in real treatments. In addition, a spherical tumor model, which is more likely to be found in clinical practice, is considered. Four cases of MNP distribution are considered for comparison in this paper: three obtained from real experimental results in agarose gel with different infusion rate, and an ideal case that is obtained using a mathematical model presented in Section 2, which considers an infusion rate tending to zero. Based on the four proposed cases, the effects of infusion rate on the temperature profile are investigated by simulation in order to obtain optimum results for treatment. In addition, two alternative approaches are proposed to improve the effective treatment area (tumor area within 42 °C and 46 °C) subject to safety constraints: multi-site injection and low Curie temperature MNPs. The low Curie temperature material considered in this study is a Fe-Cr-Nb-B alloy, which can have its Curie temperature defined in the range of interest for magnetic hyperthermia [14]. All the analyses are done considering a simulation model proposed in the paper and solved using the finite element method.

This paper is organized in five sections. Section 2 presents a theoretical framework of mass transfer and diffusion inside tissues, the modeling of an ideal MNP injection process with infusion rate tending to zero, and bio-heat transfer equation, which is used to estimate the temperature profile in the tumor region during hyperthermia. Section 3 presents how the theory described in Section 2 can be combined to create a model to predict the temperature field as a function of tissue, MNP and injection properties. For the sake of simplicity, all the development is done considering a simplified geometrical model of tumor and normal tissue, but the results can be easily extended to models with more complex geometry. Section 4 analyzes the concentration and temperature profiles inside tumor by solving the proposed mathematical model, and it also evaluates two alternative methods to improve the effective treatment area. Conclusions are drawn in Section 5.

2. Theory and method

This section illustrates the theory and mathematical method used for developing the proposed model, which can be roughly divided into two parts: one is to describe the spatial distribution of MNPs considering both the injection process (for the ideal injection case, which considers an infusion rate tending to zero) and the diffusion of MNPs inside tumor after injection, and another is to predict the temperature field for a given spatial distribution of MNPs. This discussion will be deepened in Section 4, but the proposed division is used in this section to simplify understanding of the theories that support the proposed model. Section 2.1 presents the theoretical framework used to model the interstitial pressure inside bio-tissue. Section 2.2 proposes a mathematical model for the spatial distribution of MNPs after an ideal injection process with zero infusion rate and presents a model for the diffusion of MNPs after injection inside bio-tissue. Section 2.3 presents the theory used to predict the temperature of the different tissues considered in the model during magnetic hyperthermia.

2.1. Interstitial pressure inside bio-tissue

Interstitial pressure plays an important role in the diffusion of MNPs inside the tissue after injection, which affects the magnetic fluid concentration gradient during magnetic hyperthermia. The transport of fluid in the tumor interstitium can be described by Darcy's law [15], $\boldsymbol{v} = -\kappa\nabla P_i$, where $\boldsymbol{v}$ is the interstitial flow rate, and P_i is the interstitial flow pressure. The hydraulic conductivity of the interstitial tissue is given by $\kappa = -K/\mu$, where K is the permeability coefficient, and μ is the interstitial viscosity. Assuming that the tumor is a porous media with a sink and a source of solute (MNPs) mass, the mass balance equation for an incompressible flow in steady state can be expressed as:

$$\nabla \boldsymbol{v} = \phi_B - \phi_L, \tag{1}$$

where ϕ_B is the flow source term and ϕ_L is the lymphatic drainage term. In biological tissues, the fluid source can be calculated by Starling equation as [16–18]:

$$\phi_B = \frac{L_P S}{V}(P_b - P_i - \sigma_s(\pi_b - \pi_i)), \tag{2}$$

$$\phi_L = \frac{L_{PL} S_L}{V}(P_b - P_L), \tag{3}$$

where L_P is the hydraulic conductivity of the microvascular wall, S/V is the surface area per unit volume for transport in the tumor, P_b is the static pressure of blood, is the osmotic reflection coefficient of plasma protein, σ_s is the plasma protein oncotic pressure, and π_i is the interstitial oncotic pressure, P_L is the hydrostatic pressure of the lymph, and $L_{PL}S_L/V$ is the lymphatic filtration coefficient.

After combining Darcy's law with Eqs. (1)–(3), two new expressions related to the Laplacian of the interstitial pressure for the two different regions of the model can be obtained [19]:

$$\nabla^2 P_i = \begin{cases} \frac{L_P S}{\kappa V}(P_b - P_i - \sigma_s(\pi_b - \pi_i)) - \frac{L_{PL} S_L}{\kappa V}(P_i - P_L), & \Upsilon \notin \Re \\ \frac{L_P S}{\kappa V}(P_b - P_i - \sigma_s(\pi_b - \pi_i)), & \Upsilon \in \Re \end{cases} \tag{4}$$

where Υ is the solution domain for the equations, and $\Re$ is the tumor region.

2.2. Spatial distribution of MNPs inside bio-tissue after injection

This section presents a simplified model to determine the spatial distribution of MNPs inside tumor when an injection process with a very low infusion rate is considered. If tumor is assumed to be a porous medium, the spatial distribution of magnetic fluid during injection can be determined by an approximate mathematical model [20,21], which is based on a Brinkman equation:

$$\frac{\rho_f^i}{\varepsilon_i}\frac{\partial(\mathbf{u_i})}{\partial t} = \nabla \cdot \left[-P_i\,\mathbf{I} + \frac{\mu_f}{\varepsilon_i}(\nabla \mathbf{u_i} + (\nabla \mathbf{u_i})^T) - \frac{2\mu_f}{3\varepsilon_i}(\nabla \mathbf{u_i})\mathbf{I}\right] - \left(\mathbf{u_i}K_i^{-1} + \frac{Q_{br}}{(\varepsilon_i)^2}\right)\mathbf{u_i}, \tag{5}$$