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Biomedical modeling of Magnetic Nanoparticles Fluid Hyperthermia for Cancer treatment

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Graphical Abstract

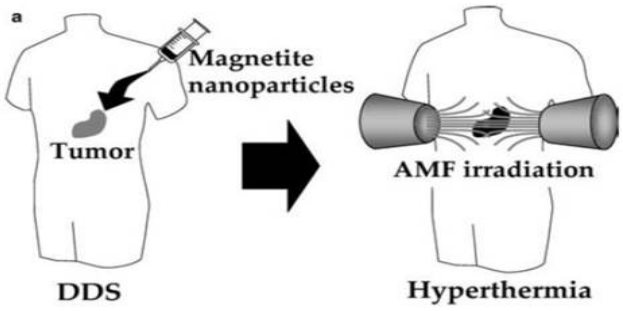

Fig 2: MNP based on polymer-coated magnetite have been used in magnetic fluid hyperthermia (MFH): A nanofluid containing the MNP is injected directly into the tumor or is injected to the tumor vasculature.

Abstract.

Magnetic Fluid Hyperthermia is called to be a promising method for cancer lesions, constituting an alternative pathway to other medical approaches. Despite of these promising possibilities, a critical problem of hyperthermia is the direct control of the heat source and the distribution of MNP in order to induce necrosis within cancerous cells with the minimum negative impact to the surrounding healthy cells. In the current project, the biomedical modeling of the process of hyperthermia is carried on for cancer cells of different geometries appealing to the modified Penne's bioheat equation and the Finite Element Method (FEM). Special attention was paid to the size and spatial distribution of nanoparticles. The results from numerical solutions have permitted to establish guidance towards optimal conditions for its use.

1. Introduction

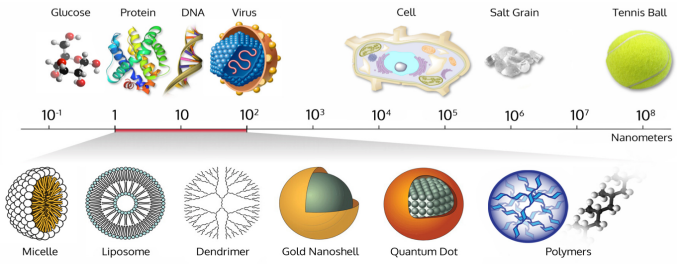

Fig 1: Nanoparticles are particles with sizes from fractions to hundreds of nanometers. They have high reactivity and a large surface to volume ratio.

Nanoparticles are particles with dimensions of the order of one nanometer (10^{-9} m) to few hundreds of nanometers. These dimensions are comparable to those observed among entities studied by molecular biology (see Fig. 1).

Among nanoparticles, Magnetic Nanoparticles (MNP) have received a considerable attention because of their potential applications in medicine, as bactericides, drug carriers, and agents for non-invasive localized therapies [1]. Cancer treatment using MNP is considered a promising therapy based on the thermal ablation of cancerous cells using the heat generated by these particles when they are placed in Alternating Magnetic Fields (AMF) (see Fig. 2) [2]. Despite of these promising possibilities, a critical problem of hyperthermia is the direct control of the heat source and the distribution of MNP in order to induce necrosis within cancerous cells with the minimum negative impact to the surrounding healthy cells. In the current project, the biomedical modeling of the process of hyperthermia is carried on for cancer cells of different geometries appealing to the modified Penne's bioheat equation and the Finite Element Method (FEM). Special

attention was paid to the size and spatial distribution of nanoparticles. The results from numerical solutions have permitted to establish guidance towards optimal conditions for its use.

2. Mathematical model and Numerical methods

In order to simulate the heating of cancer cells the modified Penne's bioheat equation [3] is used. It is a heat-type equation complemented with terms responsible for the heat exchange between the cell and blood, and also the metabolic heat and the one produced by the embedded MNP. Equations can be cast into:

$$\rho_t c_t \frac{\partial T_t}{\partial t} = k_t \nabla^2 T_t + \rho_b c_b \omega_t (T_b - T_t) + Q_t + P$$

$$\rho_h c_h \frac{\partial T_h}{\partial t} = k_h \nabla^2 T_h + \rho_b c_b \omega_h (T_b - T_h) + Q_h$$

where the sub indices t and h refer to tumor and healthy cells respectively, ρ is the tissue density, c is the specific heat for the tissue, k is the thermal conductivity, ρ_b is the blood density, c_b is the specific heat of the blood, ω_t (ω_h) is the blood perfusion rate, and T_b is blood temperature. The terms Q_t and Q_h are metabolic sources of heat for tumor and healthy cells respectively. The function P(T,H) is the rate of heat production by the MNP and includes the information about the static and dynamic components of the power dissipated by MNP. It is given by the following equation:

$$P(T,H) = \frac{1}{2}\mu_0 \chi_0 H_0^2 \omega \frac{\omega \tau_{eff}}{1 + (\omega \tau_{eff})^2}$$

where H_0 is the intensity of the applied magnetic field, ω is the frequency of the AC applied magnetic field, μ_0 is the magnetic permeability of the vacuum, χ_0 is the static component of the magnetic susceptibility, τ_{eff} is the effective relaxation time of MNP due to Brown (rotation of MNP in the viscous medium) and Neel (rotation of magnetic moments) mechanisms. The explicit mathematical expressions are:

$$\tau_{eff} = \tau_N^{-1} + \tau_B^{-1}; \quad \tau_N = \tau_0 \exp\left(\frac{KV}{k_B T}\right); \quad \tau_B = \frac{3\eta V_H}{k_B T}$$

$$\chi_0(T,H) = \chi_i \frac{3}{\xi}\left[\coth(\xi) - \frac{1}{\xi}\right]; \quad \chi_i = \frac{\mu_0 \phi M_d^2 V}{3 k_B T}; \quad \xi = \frac{\mu_0 M_d H V}{k_B T}$$

where η is the dynamic viscosity of a medium where particles are suspended, K is the effective anisotropy constant, V_H is the particle hydrodynamic volume, V is the volume of the magnetic core, M_d is the domain magnetization of the MNP, and ϕ is the volume fraction solid.

3. Results and Discussion

The parameters used for simulations are summarized in tables 1 and 2.

	Tumor	Healthy Tissue	Blood
Density – ρ (kg/m^3)	1045	1045	1060
Heat capacity – c (J/kg K)	3760	3760	3770
Thermal conductivity – k (W/m K)	0.51	0.51	----
Blood perfusion rate – ω (1/s)	0.0095	0.003	----
Metabolic heat – Q (W/m^3)	31872.5	6374.5	----

Table 1: Physical parameters characterizing each medium that were used in simulations.

Magnetic NP radius R_p= 9.5 x 10^{-9} m	Volume fraction solid ϕ = 0.071	k_B = 1.38 x 10^{23} J/K
Effective anisotropy constant K = 1.0 x 10^4 J/m^3	Dynamic viscosity η = 1.0 x 10^{-3} kg/m s	f = 300 kHz
Hydrodynamic volume V_H = 5.08 x 10^{-22} m^3	Attempt time τ_0 = 10^{-9} s	μ_0= 4π x 10^{-7} T m/A
Domain magnetization M_d = 446 kA/m	Field strength H_0 = 5518 A/m	

Table 2: Physical parameters and constants used in simulations.

The above system of partial differential equations (PDE) was discretized according to the Finite Differences and solved numerically following the Crank-Nicholson method. The inclusion of the function P(T,H) transforms the system from linear to non-linear, which demands a more careful attention. Solutions were found and plotted

with Wolfram Mathematica (Figs 3 and 4). In Fig. 3 the static magnetic susceptibility has been computed including a convolution by the distribution of particle's radii assumed to be Log-normal. Curves in red and blue correspond to particle's radii of 9.46 and 9.11 nm respectively, while the green one corresponds to 10.30 but different standard deviation, making it to appear narrower than the other two. The choice for a Log-normal distribution is based on results from [2].

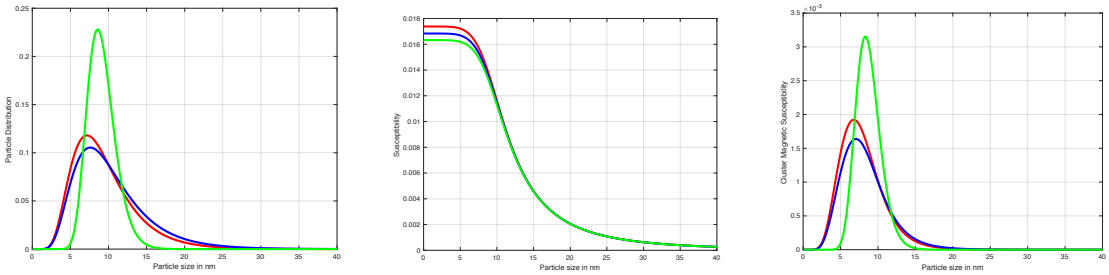

Fig 3: Computation of the Probability Distribution Function (PDF) (left) for nanoparticles, the magnetics susceptibility (center), and the cluster susceptibility (right).

The computation of the heat distribution was done for tumor cells of circular shape embeeded into a ractangular frame, as can be seen from Fig. 4. The plots show the ratio of the actual temperature to a characteristic temperature, in order the make the system of equations dimensionless. As the time goes the tumor cell is heating from the center, where the nanoparticle cluster was located. More irregular geometries are in progress and are more suitable for invasive tumor cells of rapid growth. Likewise, different nanoparticle cluster's geometries are impacting the effectivenes of using MFH.

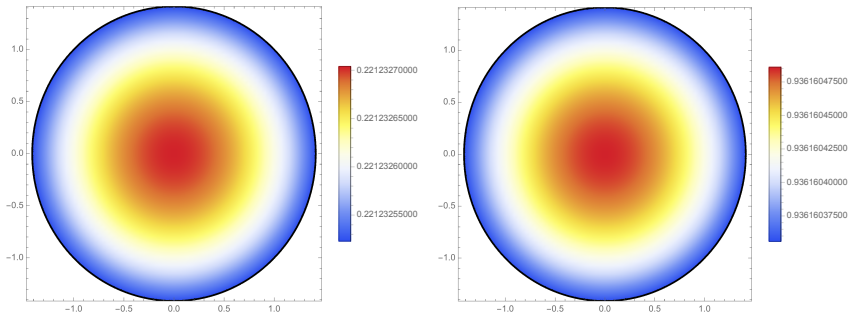

Fig 4: Numerical solution of the Modified Pennes Bio-heat equation for spherical cell model. The temperature profiles at two different moments are shown, noticing the gradual increase in temperature.

4. Conclusions

The distribution of heat inside a tumor tissue has been computed and the effect of the distribution of MNP on the intensity of the heat was determined. The heat increases initially and then drops towards the boundary of the tumor tissue preventing neighbor healthy tissues of being affected.

Acknowledgments

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