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Nanoparticles use for the Effective Hyperthermia of Liver Tumor

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Abstract:- The primary aim of this research was to evaluate the use of ferromagnetic nano particles and the use of the AC magnetic field for the treatment of cancer cells by the process of Hyperthermia. The major drawback of conventional methods for treating cancer (chemotherapy/ radiation therapy) is that it is time-consuming and not always are results guaranteed. The process is highly efficient as the nano particles generate heat locally thus preventing any damage to the surrounding healthy tissues. Also, the nano particles possess the potential to act as contrast agents for magnetic resonance imaging (MRI) making it easier to monitor the process. We try to reduce the procedure time by the introduction of magnetic nano particles which readily react to an external alternating magnetic field. This enables the nano particles to heat up to a temperature sufficient enough for tumor cell necrosis (>50deg C). The temperature spread in the tissue is studied using a COMSOL™ based Multi physics model (based on combining the Laplace, Arrhenius model and bio-heat transfer (BHTE) equation) customized for the ablation device geometry and boundary conditions. The results obtained are compared and found to be in good agreement with published text.

Keywords:- *AC Magnetic field; COMSOL Multi physics; Hyperthermia; Nano particles*

I. INTRODUCTION

Different biomedical and bioengineering applications for super paramagnetic iron oxide nano particles have been seen and used for a variety of in vivo applications. These include magnetic resonance imaging, tissue repair, immunoassay, drug delivery, detoxification of biological fluids, cell separation and hyperthermia. Magnetic fluid hyperthermia (MFH) also commonly known as the nano-cancer therapy is the process widely used in treatment of tumors. Hyperthermia offers an attractive approach for the treatment of cancer because it is associated with fewer side effects in comparison to chemo/radiotherapy, and it can be used alongside all conventional treatments. The efficacy of such trials has been demonstrated before and despite promising results, hyperthermia has not yet been established in clinical routine.

Magnetically induced interstitial hyperthermia overcome the shortcomings, especially for deep-seated and non-accessible tumors. Also, the conventional hyperthermia takes a longer time to heat the tumor cells and also causes damage to the neighbouring healthy cells. Super paramagnetic biocompatible nano particles are hence directly injected into the tumor tissue where they are stimulated by an alternating magnetic field to produce heat due to the Brownian and Ne´el relaxation processes.

Mostly the nano particles being used are composed of iron oxides such as magnetite (Fe_3O_4) and magnemite (γ-Fe_2O_3) due to their low toxicity and their known metabolic pathway. They have a crystal structure of cubic with densely packed oxygen atoms differing in the distribution of Fe ions within their crystal lattice. These magnetic nano particles tend to combine with each other to form large masses which influence their bio medical and magnetic properties in the absence magnetic field. To prevent the combining of the particles they're coated with protective shells like dextran, starch or polyethylene glycol which also helps in the interaction of the particles with the cells and also provide the functional groups for the coupling of biomolecules.

Our modelling is based on a human liver which is subjected to a liver tumor and is to be treated using Hyperthermia by magnetic nano particles. We considered the use of iron oxides as the nano particles which will be injected directly into the tumour region and then being subjected to an eternally applied AC magnetic field, it will resonate causing the nano particles to vibrate and hence generating heat. The heat being generated is only limited to a boundary around the particles and hence will not damage the living healthy cells in any manner. These nano particles are coated by a protective layer (usually a polymer) to prevent their interaction with the cells. The boundaries of different conductive tissues do not interfere with power absorption, in contrast to E-field dominant systems used in regional hyperthermia which gives it a unique property of selective thermo ablation. The temperature adopted for ablation is 50 C and magnetic field operating at frequency of 1GHz and variable field current of 15A/m. The properties of the liver tissue used for the model are provided in table 1.

Sl. No	Description	Value
1	Density, blood	1e3[kg/m^3]
2	Specific heat, blood	3639[J/(kg*K)]
3	Blood perfusion rate	3.6e-3[1/s]
4	Blood temperature	37[degC]
5	Relative permittivity, liver	43.03
6	Electric conductivity, liver	1.69[S/m]
7	Relative permittivity, dielectric	2.03
8	Relative permittivity, catheter	2.6
9	Microwave frequency	1 GHz
10	Input microwave power	10 W

Table 1: Properties of liver tissue

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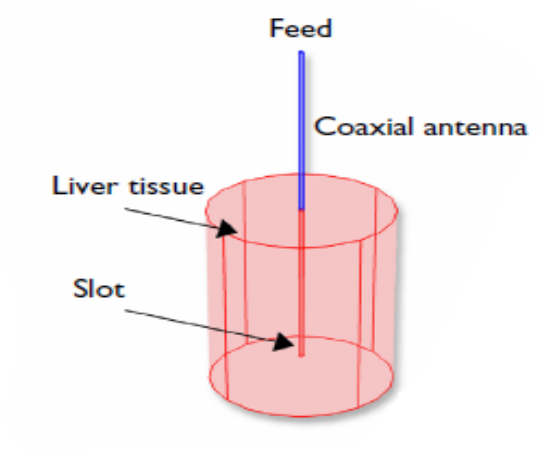
II. MODELLING

The computer model of the described problem was formulated in COMSOL Multi physics It consists of a thin coaxial cable with a ring-shaped slot measuring 1 mm cut on the outer conductor 5 mm from the short-circuited tip. For hygienic purposes, the antenna is enclosed in a sleeve (catheter) made of PTFE (polytetrafluoroethylene). The following tables give the relevant geometrical dimensions and material data. The antenna operates at 1 GHz, a slightly modified frequency from the widely used 2.45GHz in microwave coagulation therapy.

This problem does not model the interior of the metallic conductors, and it models metallic parts using boundary conditions, setting the tangential component of the electric field to zero.



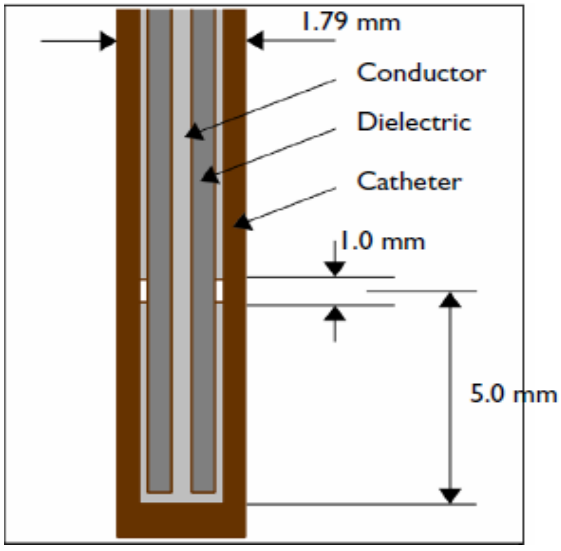


Fig. 1: The structure of the co-axial cable used in the model

The model used in this simulation makes use of the axisymmetric condition of the problem; therefore, we can model only a planar cut section and revolve it to obtain the complete model.

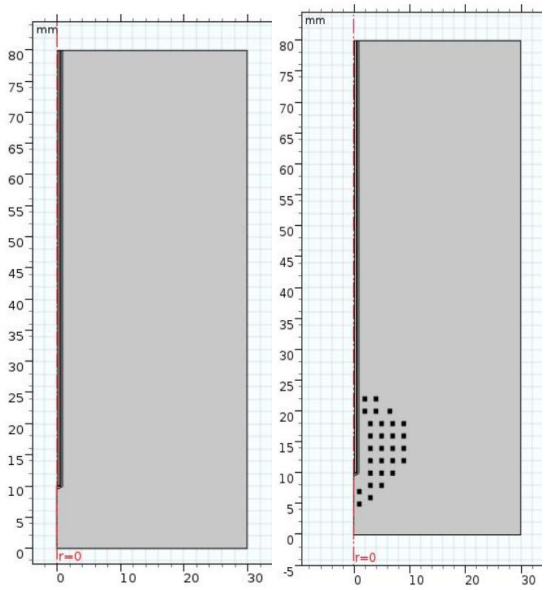


Fig. 2: Modelling of the liver tissue along with the catheter, a) without nanoparticles b)with nanoparticles

III. ELECTROMAGNETICS

The electromagnetic wave in the catheter is characterized by transverse electromagnetic waves.

$$\mathbf{E} = \mathbf{e}_r \frac{C}{r} e^{j(\omega t - kz)}$$

$$\mathbf{H} = \mathbf{e}_\varphi \frac{C}{rZ} e^{j(\omega t - kz)}$$

$$\mathbf{P}_{av} = \int_{r_{inner}}^{r_{outer}} \mathrm{Re}\left(\frac{1}{2}\mathbf{E} \times \mathbf{H}^*\right) 2\pi r dr = \mathbf{e}_z \pi \frac{C^2}{Z} \ln\left(\frac{r_{outer}}{r_{inner}}\right)$$

where r, φ and z are the cylindrical coordinates. $\mathbf{P}_{av}$ is the time average power flow in the cable, $\boldsymbol{Z}$ is the wave impedance of the cable dielectric, and r_{inner} and r_{outer} are the inner and outer radii of the dielectric, respectively. Ω represents the angular frequency, and the propagation constant, k, is given by

$$k = \frac{2\pi}{\lambda}$$

The wave equation used in the modelling of the frequency domain are given by

$$\nabla \times \mu_r^{-1}(\nabla \times \mathrm{E}) - k_0^2\left(\epsilon_r - \frac{j\sigma}{\omega\epsilon_0}\right)\mathrm{E} = 0$$

$$\mathrm{E}(r,\varphi,z) = \tilde{\mathrm{E}}(r,z)e^{-im\varphi}$$

The magnetic field domain is modelled using the basic formulas based on Ampere's Law, given by

$$\nabla \times H = J$$
$$B = \nabla \times A$$
$$E = -j\omega A$$
$$J = \sigma E + j\omega D$$

IV. HEAT TRANSFER

The time dependent heat transfer formula is given by

$$\rho C_p \frac{\partial T}{\partial t} + \nabla \cdot (-k\nabla T) = \rho_b C_b \omega_b (T_b - T) + Q_{met} + Q_{ext}$$

Where k is the thermal conductivity (W/(m·K)), ρ_b is the density of blood (kg/m^3), C_b is the specific heat capacity of blood(J/(kg.K)), omega$_b$ represents the blood perfusion rate(1/s), and blood temperature T_b. The heat source from metabolism, Q_{met}, and Q_{ext} is an external heat source, both whose units are W/m^3.

The tissue damage integral gives us a fair idea about the degree of tissue injury, based on the Arrhenius equation:

$$\frac{d\alpha}{dt} = A \exp\left(-\frac{\Delta E}{RT}\right)$$

Where ΔE is the activation energy for irreversible damage reaction(J/mol), and A is the frequency factor(s^{-1}).

V. SIMULATION

The above-described problem has been simulated in COMSOL Multi physics. The study used in this particular problem is a frequency study to analyze the electromagnetic fields, followed by a time study step to determine the tissue temperature and damage over a period of time. The heat generated due to the electromagnetic fields was coupled with the biological tissue (or tumor) to simulate the heating. The initial condition of the entire setup was taken to be equal to 310.15 K (T_blood), the same as the arterial blood temperature.

VI. RESULTS AND DISCUSSIONS

The figures below portray the effect of heating of the liver tumor with and without nanoparticles respectively.

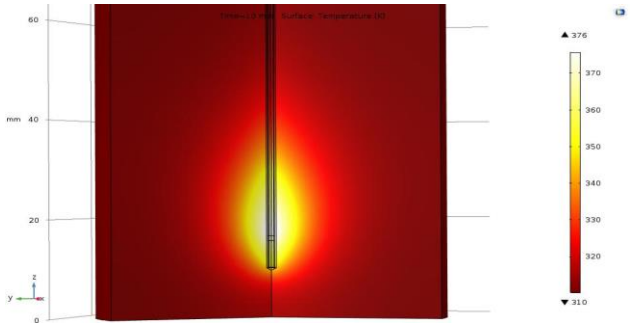


Fig. 3: Temperature distribution after 10 mins of hyperthermia

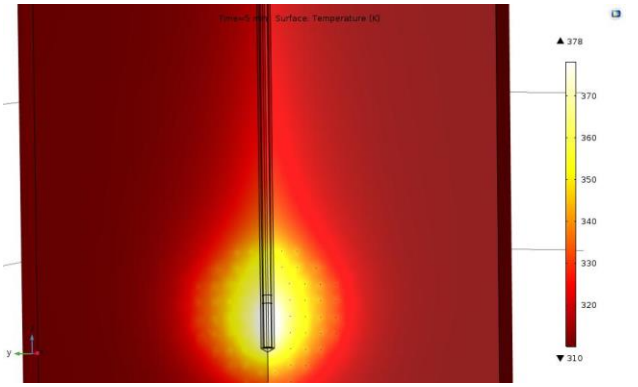


Fig. 4: Temperature distribution after 5 mins of nano particles aided hyperthermia

From the results, it is evident that the use of nano particles, considerably reduces the time required to cause cell necrosis. In this simulation with nano particles, the time required reduced by 50%, and also the nano particles enable uniform heating throughout the tumor tissue, as opposed to the original model where the localized heating occurs at a greater rate near the electrode.

We can see that the temperature required of cell necrosis (>323 K) has been reached in the nano particles aided model in 5 mins as compared to 10 mins of hyperthermia without nano particles. This simulation can hence throw light on the importance of this technique, for further developments.

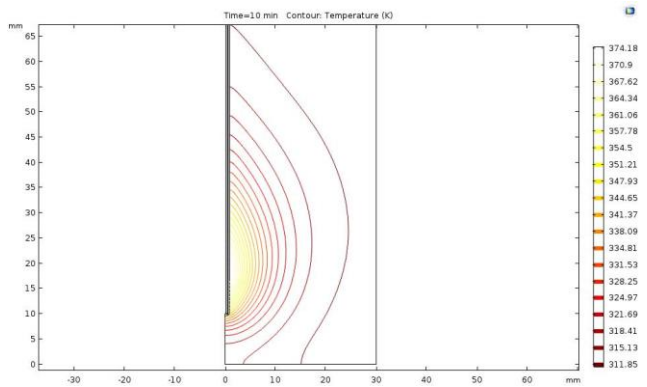


Fig. 5: Isothermal contours of regular hyperthermia

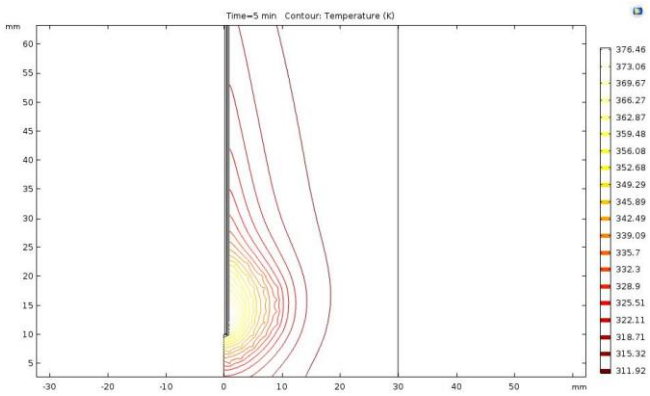


Fig. 6: Isothermal contours of nano particles aided hyperthermia

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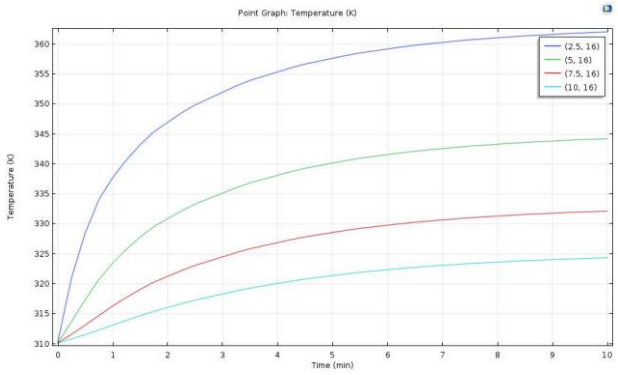
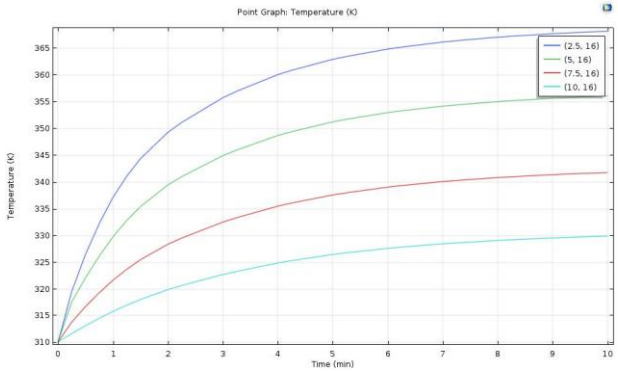
The above isothermal contours show the temperature distribution around the electrode in a detailed manner.



(a)



(b)

Temperature distribution at distances of 2.5mm, 5mm, 7.5mm and 10mm away from the electrode at different points of time (a) with regular hyperthermia (b) with nano particles aided hyperthermia

Even though much research has to be done on the safe use of super paramagnetic iron oxide nano particles on the internal organs of the human body, and on the safe removal of the nano particles from the body after the therapy, this technique is an advancement over the regular hyperthermia in the sense that it takes considerably lesser time while ensuring uniform cell necrosis around the electrode

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