Nanoparticles in enhancing microwave imaging and microwave Hyperthermia effect for liver cancer treatment

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Abstract: Hyperthermia therapy is a promising therapy for liver cancer treatment that utilizes electromagnetic waves to heat the tumor zone to preferentially kill or minimize cancer cells. Nevertheless, it’s a challenge to realize localized heating of the cancer tissue without harming the surrounding healthy tissue. This research proposes to utilize nanoparticles as microwave absorbers to enhance microwave imaging and achieve localized hyperthermia therapy.

A realistic 3D abdomen model has been segmented using 3D Slicer segmentation software, and then the obtained segmented CAD model exported to Computer Simulation Technology (CST STUDIO) for applying the Finite Element Modeling (FEM). Next investigating both imaging and treatment capability. Finally, the specific absorption rate (SAR) and temperature distribution were computed without nanoparticles and with different types of nanoparticles such as gold (GNPs) and silver nanoparticles at frequency 915 MHz. By comparing the achieved results, it was seen that Silver nanoparticles can make a great enhancement in raising the temperature. However, this result was unsatisfactory but, after adding gold nanoparticles the temperature exceed 42°C, at frequency 915 MHz which is achieving the hyperthermia treatment without harming the nearby healthy tissue, GNPs also can achieve a great enhancement in SAR result

Keywords: liver cancer, microwave imaging, hyperthermia

1 Introduction

In 2019, an expected 42,030 adults (29,480 men and 12,550 women) in the United States will be diagnosed with primary liver cancer. Since 1980, the percentage of liver cancer has tripled. Between 2006 and 2015, the number of cases diagnosed with the disease increased by around 3% annually. Men are about 3 times more likely than women to be diagnosed with the liver cancer [1]. Severe patients that cannot undergo surgical resection are eligible for hyperthermia which is a new therapeutic method that consists in heating the tumor cells in order to make selective damage. Final temperatures can range between 42°C to 45°C (mild hyperthermia) [2].

Currently, two frequencies – 915 and 2.4 GHz – are utilized in microwave hyperthermia; the frequency of 2.4 GHz is commonly applied in the clinic. Compared with 2.4 GHz microwaves, 915 MHz microwaves have a larger penetration depth. Besides, the energy attenuation of 915 MHz microwaves is less than that of 2.4 GHz microwaves and more electromagnetic energy may convert into heat energy. Therefore, 915 MHz microwaves can provide a larger hyperthermia zone [3, 4].

Nevertheless, achieving localized hyperthermia of the cancer cells without harming the nearby healthy tissue still challenges [5]. This study proposes to utilize nanoparticles as microwave absorbers to realize localized heating under microwave radiation which has been investigated for prevention, treatment, and early diagnosis of cancer, since nanoparticles can accumulate around or inside malignant regions, to aid localized heating only affecting tumors. Approaches to nanoparticle-mediated hyperthermia include plasmonic photothermal therapy (PPTT), magnetically induced heating [6], and microwave irradiation. For PPTT methods, gold nanoparticles can possess greatly enhanced visible and near-infrared light absorption due to the phenomenon of surface Plasmon resonance. Unfortunately, the penetration depth of near-infrared light in the human body is only a few millimeters due to notable scattering and attenuation of light by biological tissues. Furthermore,
the toxicity of a surfactant utilized in gold nanoparticle synthesis can degrade membranes and peptides.

Magnetically induced heating takes advantage of magnetic nanoparticles excited by the external electromagnetic (EM) field with a much longer wavelength, which can penetrate deeper through the human body [7]. Under the EM field, magnetic nanoparticles can perform magnetic hysteresis [8], Néel or Brown relaxation, and magnetic resonance, coupling the external EM field power into nanoparticles to generate heat [9]. However, the absorption efficiency of these magnetic nanoparticles highly depends on their size and morphology, which are difficult to manage due to their complex chemical synthesis processes: the intrinsic complex synthesis limits their optimal structures. Furthermore, besides the problem of particle aggregation, biocompatibility remains another notable hurdle for magnetic nanoparticle hyperthermia. The third type of nanoparticle-based hyperthermia therapy, called microwave irradiation, is based on microwave absorbers with high conductivity. The penetration depth of microwaves in the 0.9–3 GHz range into the human body can be several centimeters, which is suitable for medical applications. Comparing to the other mentioned methods [10, 11].

Current efforts have shown that numerical simulation of nanoparticles assisted thermal therapy can be used as a pre-treatment planning strategy which can help to predict temperature distribution within the body to optimize the treatment parameters before the actual heating operation [12, 13]. The main weakness with the current numerical simulation is that the model has been often assumed with a simple phantom geometry rather than the actual geometry [14]. One improvement to the current simulation model is to use three-dimensional (3-D) anatomically realistic abdomen model geometry to strength the accuracy of heat transfer models for accurate prediction of temperature distribution. The use of 3-D realistic abdomen model geometry is a key requirement for accurate prediction of temperature distribution during simulation of the heat transfer process.

This paper explains, through computer simulation of the real human model the use of microwave antennas in microwave imaging of tumor inside liver and it also predicts the temperature distribution in the liver; inside and outside the tumor during hyperthermia with and without using nanoparticles.

2 Physical phenomena during microwave tissue hyperthermia

2.1 Microwave Absorption in Tissue

The complex geometries and tissue properties involved in simulation of microwave hyperthermia therapy, especially perfusion term, makes computer simulations an ideal choice over analytical solutions which require many simplifying assumptions. The present work is based on EM numerical analysis approach of FEM, because FEM uses piecewise approximation to solve the governing bioheat transfer equation. Geometric irregularities and regional heterogeneity are more easily handled by FEM.

The ultimate goal of computer models for microwave tissue hyperthermia is to induce tissue damage, which is a function of the time-temperature, and for this temperature profile in tissue during a hyperthermia procedure depends upon two physical phenomena: (a) interaction of microwaves with tissue and (b) heat transfer in tissue [15]. While considering the interaction of microwaves with tissue, propagation and absorption of microwaves in tissue is governed by Maxwell’s equations, stated in Equations (1)–(4).

\[ \nabla \cdot D = \rho_{\text{free}} \]  
\[ \nabla \cdot B = 0 \]  
\[ \nabla \times E = -\frac{\partial B}{\partial t} \]  
\[ \nabla \times H = J + \frac{\partial D}{\partial t} \]  

Where \( D \) [C/m²] is electric flux density, \( B \) [T] is magnetic field, \( E \) [V/m] is electric field strength, \( H \) [A/m] is magnetic field intensity, \( \rho_{\text{free}} \) [A/m²] is current density and \( J \) [C/m²] is free charge density.

The EM fields radiations radiated in a given tissue by an appropriate antenna can be determined by solving the Maxwell’s equations, with the knowledge of tissue electromagnetic properties (permittivity and conductivity) and appropriate initial and boundary conditions, in order to develop accurate models of the hyperthermia process.

The absorption of electromagnetic power in tissues is a function of their material properties, conductivity \( \sigma \) [F/m] and dielectric permittivity \( \varepsilon \) [S/m].
2.2 Attenuation effect and penetration depth

Microwave passes through the abdomen of the human body, then through liver; it will attenuate, resulting in the decrease of the energy obtained by the liver. Interaction between the microwave and a liver may be obtained with knowledge of the relative complex permittivity $\varepsilon^*$ of that material, given by the relation [16].

$$\varepsilon^* = \varepsilon' - j\varepsilon''$$  \hspace{1cm} (5)

Where $\varepsilon'$ is the dielectric constant and $\varepsilon''$ is the dielectric loss factor given by:

$$\varepsilon'' = \frac{\sigma}{2\pi f\varepsilon_0}$$  \hspace{1cm} (6)

$f$ is the frequency in Hertz.

From equations (5) and (6) it is possible to derive the quantity of plane wave skin depth ($\delta$) which is defined as the distance measured from the surface to a point in the bulk material at which the amplitude of the electric field of an electromagnetic signal has been reduced by a factor of $1/e$ of its surface value. The relation is given by:

$$\delta = \frac{1}{\alpha}$$  \hspace{1cm} (7)

Where the attenuation coefficient $\alpha$ is given by:

$$\alpha = \omega \sqrt{\frac{\mu \varepsilon}{2} \left[ \sqrt{1 + \left( \frac{\sigma}{\omega \varepsilon} \right)^2} - 1 \right]}$$  \hspace{1cm} (8)

and $\mu$ is the material permeability given by the product of relative permeability $\mu_r$ and the permeability of free space $\mu_0$, $\varepsilon$ is the material permittivity given by $\varepsilon_r\varepsilon_0$, $\sigma$ is the material conductivity [16].

2.3 Heat Transfer in Tissue

The temperature profile in tissue during hyperthermia is obtained by solving a bioheat equation. The most widely used bioheat equation for modeling thermal therapy procedures is the Pennes’ bioheat equation [13].

$$\rho\varepsilon \frac{\partial T}{\partial t} = \nabla \cdot (K \nabla T) + Q + Q_p + Q_m$$  \hspace{1cm} (9)

Where $\rho$ [kg/m$^3$] is mass density, $c$ [J/kg*K] is specific heat capacity, $k$ [W/m-K] is thermal conductivity, $T$ [K] is temperature, $Q$ [W/m$^3$] is the absorbed electromagnetic energy, $Q_p$ [W/m$^3$] is the heat loss due to microvascular blood perfusion, and $Q_m$ [W/m$^3$] is metabolic heat generation. The blood perfusion term, $Q_p$ is given by (10).

$$Q_p = \omega_b c_b (T - T_b)$$  \hspace{1cm} (10)

Where $\omega_b$ [kg/m$^3$ * s] is blood perfusion rate, $c_b$ [J/kg*K] is the specific heat capacity of blood and $T_b$ [K] is blood temperature. Commonly, $Q_m$ is neglected as its magnitude is much smaller than other terms in this equation. The absorbed electromagnetic energy, $Q$, is computed from the electromagnetic field distribution in tissue and can be written as (11).

$$Q = \frac{1}{2} \sigma |E|^2$$  \hspace{1cm} (11)

As is the case with the electromagnetic model characterization of tissue thermal properties is required for accurate prediction of the temperature profile.

3 Methods

3.1 Antenna Design

Antenna Magus (AM) is antenna design software product. It takes on a totally new method to designing antennas. Its tools assist researchers with antenna design. AM is the first design tool of its kind. Its huge searchable collection of antennas can be explored to find, design and export models of designed antennas to CST Studio. It reduces the time to find and assess feasible antenna approach for biomedical application, providing reliable initial designs and confirmed simulation models. It matches CST Studio very well, as important tools within the antenna synthesis process [17, 18].

A planar Archimedes spiral is used also called planar Archimedean spiral (PAS) antenna, it considered to be frequency independent. However, in practice it has finite bandwidth due to their finite arm lengths and finite inner gap width. The minimum frequency is determined by the outer diameter of the spiral and the maximum frequency by the inner diameter and the precision at the feed region. PAS is inherently circularly polarized with relatively constant input impedance and radiation patterns over wide frequency ranges [19].

The arms of PAS antenna have a constant growth rate as defined by the following equation:

$$r = b + r_0 \varphi$$  \hspace{1cm} (12)

where the constants $b$ is the starting radius and $r_0$ is the growth rate. The angle is represented by the independent variable, $\varphi$ Figure 1 shows PAS antenna design sketch and gain pattern, Figure 2 show shows Abdomen model using Self Complimentary Archimedes antenna

The PAS antenna has a substrate made of Rogers RT 5880 which has a dielectric constant of 2.2 and thermal conductivity value 0.2 W/K-m. The thickness of the substrate is
Figure 1: PAS antenna (a) Sketch, (b) Gain pattern

Figure 2: Abdomen model using PAS antenna

Table 1: PAS antenna Dimensions and specification

| Antenna Specifications | Dimensions / specification |
|------------------------|---------------------------|
| $W_a$                  | 11.49 mm                  |
| $S_a$                  | 11.49 mm                  |
| $D_0$                  | 429.4 mm                  |
| $D_i$                  | 27.26 mm                  |
| Polarization           | Circular                  |
| Radiation pattern      | Bi-directional            |
| Gain                   | 4 : 6 dBi                 |

1 mm from the ground plane. The back side of the substrate contains the partial ground plane, the antenna is based on a 50 $\Omega$ semirigid copper-Teflon coaxial cable the ground plane is made up of copper which is a lossy metal, Table 1, demonstrate PAS Antenna Specifications.

Antenna designing steps:

- Investigate reflection coefficient $S_{11}$ parameter variations along with antenna parameter changes. By this way, we obtain the relation between $S_{11}$ and antenna’s structural parameters [20].

$$S_{11} = 10\log_{10}\frac{P_r}{P_i} \quad (13)$$

Where $P_r$ is the reflected power and $P_i$ is the input power. Smaller $S_{11}$ indicates greater power coupled to the liver tissue.

- Computation of the EM field distribution. The CST STUDIO is applied in the computation process an adaptive solution is applied. The maximum number of passes is set to 10 and maximum delta E per pass and refinement per pass is set to 0.2 and 20%.

- Calculation of the specific absorption rate (SAR distribution), first, we calculate the electric field around
the antenna and parameter \( S_{11} \) (the reflection coefficient). Next, we calculate the SAR distribution. The SAR takes a value proportional to the square of the electric field around the antenna and is corresponding to the heating source generated by the electric field in the tissue.

\[
SAR = \frac{\sigma E^2}{\rho} \quad (14)
\]

- We investigated \( S_{11} \) as a function of frequency changes along with antenna's different structural parameters. We obtained the relation between \( S_{11} \) and antenna’s structural parameters. The result shows that proper changing the space of adjacent spiral circle or the spiral circle numbers of the antenna makes antenna to work at broadband frequency. And \( S_{11} \) decreases when the width of spiral wire decreases.

- An optimized PAS was designed. Its SAR distribution in tissue at 915 MHz was simulated. As a result, distribution of SAR is convenient control when work frequency 915 MHz.

3.2 Modeling procedure

3.2.1 3D Human Abdomen Model Reconstruction

The first step into the construction of a realistic model was to build a proper geometry based on anthropomorphic data. This was accomplished by collecting actual anatomical CT images properties.

| Plane    | Number of slices | Resolution |
|----------|------------------|------------|
| Axial    | 455 slices       | 1 mm       |
| Sagittal | 399 slices       | 1 mm       |
| Coronal  | 399 slices       | 1 mm       |

Figure 3: Direction of 3 plans data set

Figure 4: Fully automated segmentation for bone in 3D Slicer

Figure 5: Manual segmentation for liver in 3D Slicer

Figure 6: Semi-Automated segmentation for abdomen in 3D Slicer
images of the abdomen area in a real patient. It consists of four different tissues: fat, liver, bone and cancer. Each of these tissues which had been determine as 3D shapes and dimensions by using powerful software 3D Slicer.

The provided data set is consisting of images in all the three planes axial, sagittal and coronal. Figure 3 shows the direction of the 3 planes used in data set Table 2. list the used DICOM images properties in each plane.

After building each segment for different tissues, we convert these segments into 3D shapes as STL file in order to use these shapes for our simulation, where STL is abbreviation of stereo lithography which is a CAD software created by 3D Systems, STL files describe only the surface geometry of a three-dimensional object without any representation of color. Figure 4, 5, and 6 shows the 3D segmentation of bone, real human liver, and abdomen model respectively Figure 7 shows the 3D Longitudinal sector of real human bone and abdomen model, and a Flow chart for segmentation procedures.

3.3 Finite Element Modeling (FEM)

The proposed 3D real human abdomen model was developed using Computer Simulation Technology (CST Studio) which is a high-performance full-wave electromagnetic emulator for 3D volumetric modeling that takes advantage of the familiar Microsoft Windows graphical user interface. It integrates simulation, visualization, solid modeling, and automation, are unique, where solution to 3D EM problems is accurately obtained. Dielectric properties at frequency 915 MHz and thermal properties of the proposed 3D real human abdomen model [8] are shown in Table 3 and Table 4.

The proposed 3D real human abdomen model was developed using Computer Simulation Technology (CST Studio) which is a high-performance full-wave electromagnetic (EM) simulator for 3D volumetric modeling that takes advantage of the familiar Microsoft Windows graphical user interface. It integrates simulation, visualization, solid modeling, and automation, are unique, where solution to 3D EM problems is accurately obtained.

When a 3D abdomen model embedded in CST the resulting mesh elements total number was about 110 million tetrahedral. To save time and cash memory used we utilize a simple model with fewer curvature, in addition to a spherical tumor with 1 cm was inserted at location 0, 0, 2 (x,y,z) instead of actual tumor in CT image which its volume was larger than 3.5 cm, as shown in Figure 8 also the aim of this is to detect the ability of a microwave imaging to enhance tumor detection and diagnostic accuracy.
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Table 3: Dielectric properties of human tissue and cancer at 915 MHz

| Tissue   | \(\varepsilon_r\) | \(\sigma\) (S/m) |
|----------|------------------|-----------------|
| Fat      | 5.2801           | 0.10452         |
| Bone     | 20.756           | 0.34353         |
| Liver    | 46.764           | 0.86121         |
| Tumor    | 38.836           | 0.595           |

Where \(\varepsilon_r\): Electrical permittivity, \(\sigma\): Conductivity

Table 4: Thermal properties of tissue and cancer

| Tissue   | \(\rho\) [kg/m\(^3\)] | \(C\) [J/Kg] | \(K\) [W/m] |
|----------|------------------------|--------------|-------------|
| Fat      | 910                    | 2973         | 0.201       |
| Bone     | 1850                   | 1256         | 0.11        |
| Liver    | 1020                   | 3816         | 0.469       |
| Tumor    | 1000                   | 3500         | 0.570       |

4 Results and Discussion

4.1 Microwave Imaging

Currently X-ray-based imaging systems suffer from low contrast between malignant and healthy tissues in liver. Microwave Imaging shows a higher contrast between the aforementioned tissues and therefore can enhance tumor detection and diagnosis accuracy [21].

Exposing the liver to microwaves will cause the liver tissues to absorb some of the incident energy. The microwave energy travels through the liver model from a transmitter (planar Archimedes spiral) and is detected at SAR monitor in CST Studio located on the other side of the liver which acts as a receiver. Instantaneously, reflections may be recorded at the transmitter. Microwaves traveling through the tumor experience a change in material dielectric property which leads to scattering of the incident wave. This scattering modifies the energy detected at the SAR monitor and the transmitter also. Finally, images are formed from the information of detected energies. This implies at least two approaches for creating microwave images which are tomography and radar-based technology.

In this work, we present the imaging results of our Microwave imaging system that is equipped with a PAS antenna. Moreover, to demonstrate the safety of our system for human subject tests, we simulated the Specific Absorption Rate (SAR) in a realistic liver tissue model and compared the resulted values with ICNIRP Standard [16].

The operating frequency in this simulation is 915 MHz the model is simulated by running the high frequency transition solver in CST Microwave Studio, set for an accuracy of ~50 dB. These responses represent the state of the model without Nanoparticles as shown in Figure 9. The SAR was computed in the model at frequency 915 MHz a centrally located region of SAR (0.063 W/kg) is observed (green color). This SAR region coincides with the cancer placed at the center of the liver model.

4.2 Effect of Gold nanoparticles on Specific Absorption Rate

A spherical gold nanoparticle with a diameter of 100 nm was embedded. The SAR was recomputed in the model after adding nanoparticles. We use GNPs in our simulation. The SAR value (2 W/kg) shows a great enhancement after adding GNPs as shown in Figure 10.

Figure 9: SAR by using (PAS) antennas at frequency 915 MHz
4.3 Temperature Prediction

Two temperature monitors were used to record temperature increase in the liver tissue which illuminated by PAS antenna. These temperature measurements were recorded inside and outside the tumor with and without nanoparticles. One monitor was placed at the center of the tumor; the other monitor was placed at 2 cm from the first monitor. Figure 11 shows the temperature distribution in the human liver model obtained from CST. With Presence of nanoparticles, there is an insignificant temperature increase in the cancer to cause any damage to the tissues.

4.4 Effect of different nanoparticles on temperature measurement

4.4.1 Effect of silver nanoparticles

Spherical Silver nanoparticles (AgNPs) with a diameter of 100 nm were embedded around cancer at frequency 915 MHz and the transient temperature was once again studied.

Figure 12 shows that the temperature at the cancer region is now 40.5°C at frequency 915 MHz while the temperature of healthy tissue still not affected which is a great enhancement after adding AgNPs However; the results were
unsatisfactory and did not achieve the required temperature.

4.4.2 Effect of gold nanoparticles

Gold nanoparticles were injected around the cancer at frequency 915 MHz and then transient temperature was once again studied. These results in Figure 13 shows that the temperature at the cancer region is now 42.1°C at the same frequency and also the temperature of healthy tissue still not affected which is a great enhancement after adding GNPs which is achieved the desired temperature for hyperthermia.

Results of SAR and Hyperthermia analysis at the end of the simulation were summarized Table 5, by analysis these results it note that:

- SAR has a better value (2 W/kg) when using GNPs at 915 MHz frequency.
Table 5: SAR and Hyperthermia Results at 915 MHz

| Result       | SAR W/Kg | Hyperthermia Without Nanoparticles (Temperature °C) | Hyperthermia With Nanoparticles (Temperature °C) |
|--------------|----------|------------------------------------------------|-------------------------------------------------|
|              | Without NPs | With GNPs | Inside Cancer | Outside Cancer | Inside Cancer | Outside Cancer | Inside Cancer | Outside Cancer |
| SAR          | 0.063    | 2        |              |                |              |                |              |                |
| Hyperthermia | -        | -        | 38.6         | 37.5           | 41.9         | 38.5           | 42.2         | 38.3           |

- Achieving hyperthermia (41.9°C) when using AgNPs at 915 MHz frequency, while the temperature in the surrounding healthy tissue is in a safe limit (38.5°C).
- Achieving hyperthermia (42.2°C) when using GNPs at 915 MHz frequency, while the temperature in the surrounding healthy tissue is in a safe limit (38.3°C).

Figure 14 compares results of hyperthermia at 915 MHz frequency, it notes that without using NPs (black) it reaches a value of 38.6°C, when using AgNPs (blue) it reaches a value of 41.9°C inside the cancer, while when using GNPs (green) the temperature reaches a value 42.2°C inside the cancer, which is archived hyperthermia treatment, without harming the nearby healthy tissue since the temperature outside cancer is 38.3°C.

5 Conclusion

The challenge in hyperthermia treatment is to heat the cancer to a therapeutic temperature without harming the nearby healthy tissue. The results presented in this paper show that microwave imaging and hyperthermia treatment can be enhanced by the use of GNPs.

A system with a microwave applicator (PAS antenna) at 915 MHz, Nanoparticles and Two temperature monitors in and outside the cancer were modeled to accurately study microwave imaging and hyperthermia treatment for cancerous tissues in the realistic liver model.

Simulated results were obtained using CST Studio and values for the SAR and transient temperature in the healthy tissue and the cancer were presented. Using Penne’s bio-heat transfer equation and comparing results with and without Nanoparticles it was seen that Silver nanoparticles can make a great enhancement in raising the temperature. However, this result was unsatisfactory and did not achieve the required temperature but, after adding gold nanoparticles the temperature exceed 42°C which is achieving the hyperthermia treatment without harming the nearby healthy tissue.

GNPs also can achieve a great enhancement in SAR result and this result show that the system is safe for test on human subjects, in accordance with Europe standards.

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A Additional figures

Figure A1: Abdomen segmentation in 3D slicer

Figure A2: Liver segmentation in 3D slicer
Figure A3: Liver segmentation in 3D slicer

Figure A4: Three plan of segmentation in 3D slicer
Figure A5: Segmented liver model in 3D Slicer

B Multimedia