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Mathematical Modelling of Breast Cancer Thermo-therapy Treatment: Ultrasound-based Approach

[1]**Oluwafemi O. Olayebi**
Department of Chemical Engineering,
Federal University of Petroleum Resources,
Effurun, Delta State, Nigeria
e-mail: olayebi.oluwafemi@fupre.edu.ng

[2]**Stephen C. Agbobu**
Department of Mechanical Engineering,
Niger Delta University,
Wilberforce Island, Bayelsa State, Nigeria
e-mail: sagbobu@gmail.com

[3]**Iwekumo Wauton**
Department of Chemical and Petroleum Engineering,
Niger Delta University,
Wilberforce Island, Bayelsa State, Nigeria
e-mail: tariebi2015@gmail.com

[4*]**Ademola S. Olufemi**
Department of Chemical and Petroleum Engineering,
Niger Delta University,
Wilberforce Island, Bayelsa State, Nigeria
e-mail: adestanford.olufemi @gmail.com

***Abstract*— Breast cancer is a disease which affects the cells in the breast, it caused by an uncontrolled division of abnormal cells that can be either benign or malignant in the breast tissues. In this study, models of an ultrasound spherical phased tissue that can be used for thermotherapy treatment of tumours in the intact breast are presented. The first analytical model, examines the temperature rise in the tissue due to ultrasound without metabolic heat source and the heat deposition in the biological tissues and also 3-Dimensional temperature distribution during ultrasound thermotherapy. In the second model a modified heat transfer equation was used to compute temperature profiles with the addition of metabolic heat source in the tissue. The presented models show that for a comparatively small tumour (2 cm in diameter) and a point heat source set at 45 ^0C, only a small portion in the internal part of the tumour would be damaged and/or destroyed within a duration of about 100 seconds. The application of mathematical techniques can be used in the prediction of the temperature profile in thermotherapy used for the treatment of breast cancer**.

***Keywords*— Breast cancer; Mathematical model; Ultrasound thermotherapy; Bio-heat**

I. INTRODUCTION

Breast cancer is a major cause of death in women, and its incidence is increasing every day. Treatment approaches of breast cancer include radiology, targeted therapy, chemotherapy, surgical removal of the tumour, etc. However, these methods have many negative effects that make patients feel unbearable pain and inflict deep anxiety. For years now, there has been a struggle to discover new methods to fight against breast cancer [1].

Thermotherapy is an old therapy of treatment that gives a new hope and when combined with engineering techniques proves to be one of the best cancer treatment options [1]. Thermotherapy, also called thermal therapy or hyperthermia (HT), is a mode of cancer treatment in which body tissue is subjected or exposed to high temperatures of up to 45 °C, using external and internal heating equipment/devices to damage and/or kill cancer cells for a defined period of time. The extent of temperature elevation associated with thermotherapy is usually a few degrees above normal temperature (37–45 °C) [2] and is almost always used with other forms of cancer therapy such as radiation and/or chemotherapy. Research has shown that high temperatures can damage or kill cancer cells, usually with minimal injury to normal tissues in the surrounding, making it much safer than traditional treatment therapies. In ACS [3], it is proposed that by killing cancer cells and damaging proteins and structures within the cells, thermotherapy may shrink tumours, making the cells more sensitive to radiation therapy and/or chemotherapy (CT).

Furthermore, many clinical studies show that high temperature thermotherapy alone can be used for selective tissue destruction as an alternative to conventional invasive surgery. Due to the heterogeneous and dynamic properties of tissues, including blood perfusion and metabolic heat generation, it is important to present models of the temperature change during the treatment of tumours [1].

The major challenge in thermal therapy is delivering the appropriate amount of heat to the correct part of the patient's breast, because external application of heat at
excessive temperature may result in surface burns, swelling, bleeding, infection, heart problem or even death especially when perfused [2].

The effectiveness of thermotherapy depends greatly on the temperature achieved during the treatment. Another important factor is the duration of the treatment and temperature of the surrounding tissue [2]. However, the monitoring of the temperature requires invasive needles with tiny thermometers to be inserted into the treatment area to ensure that the desired temperature is reached and the surrounding tissue not be damaged. Imaging techniques such as CT scans are also required and can be expensive to use for clinical study purposes. Hence, a mathematical model can be used for understanding the temperature profile of the tumor.

Various mathematical and analytical approaches have been developed over three decades, for the purpose of understanding the interaction of ultrasound with biological tissues and the lesion development during focused ultrasound surgery. The technique of thermal therapy presented in this work is the local thermotherapy, in which heat is applied to a small area using a focused ultrasound beam. Firstly, analytical models calculating heating patterns due to therapeutic transducers were developed. Secondly, computer modelling to determine the temperature distribution of a given treatment and to plan future hyperthermia treatments have been applied [4].

A number of studies have focused on modelling the heating from single exposures from axially symmetrical transducers, such as spherical bowls, and subsequent lesion formation. Lizzi and Ostromgilsky [5], developed a simple analytical model for breaking down the heating volume into a series of cylinders that were used as elemental heat sources. On the other hand, a model for tumour therapy based on the bio-heat equation [6] was developed to calculate intensity patterns using a one-dimensional transformation of the diffraction equation. Temperatures were computed using a successive over-relaxation method, assuming uniform perfusion [7]. Lu *et al* [8], proposed a model with a simplified ultrasound beam model which examined the treatable domain formed by the tumour size and optimal driving frequency and tumour depth and to simulate the specific absorption rate (SAR) distribution for the thermal treatment of bone tumour. However, in this study, the mathematical modelling of heat transfer for an ultrasound beam on the breast cancer tumor is advanced.

II. MATHEMATICAL MODEL

As previously cited in order to have an effective treatment, resulting in a reduction of tumor size, the tumor must reach a temperature of approximately 45 ^{0}C. In order to simplify the model, the tumor is analyzed as a perfect sphere with radius, r = 1 cm = 0.01 m. It is assumed that the ultrasound beam is to be perfectly focused, in other words, the beam only applies heat at a point in the center of the tumor and any other heat energy from the beam is negligible.

In this work, the Pennes' bio-heat equation, which is the general heat diffusion equation with additional terms for perfusion of blood and metabolic heat is used, in spherical coordinates, as follows:

$$\frac{\rho C_p \partial T}{k \partial t} = \frac{\partial}{r^2 \partial r}\left(r^2 \frac{\partial T}{\partial r}\right) + q_P + \frac{q_m}{k} \quad (1)$$

Where ρ is the density of the tumour, Cp is the heat capacity of the tissue, k is the thermal conductivity of tissue and q_m is the metabolic heat term (or heat that the tumour generates from its metabolic processes). q_P is defined as heat perfusion or the heat that is carried away from the tumour site by arterial blood flow and is defined as: $\frac{\omega * \rho b * C_p b}{k}(T_\infty - T)$ where ω = perfusion rate of blood, T_∞ = arterial temperature, T = local tissue temperature, ρb = density of blood and $C_p b$ = heat capacity of blood. This means that the temperature profile with respect to time is dependent on the diffusivity of heat through the tumour as well as how much heat is exchanged through the arteries in addition to metabolic heat generation.

Dividing equation (1) by $\frac{\rho C_p}{k}$, and simplifying further,

$$\frac{\rho C_p \partial T}{k \partial t} = \frac{k \partial}{\rho C_p r^2 \partial r}\left(r^2 \frac{\partial T}{\partial r}\right) + \frac{k q_P}{\rho C_p} + \frac{q_m}{\rho C_p} \quad (2)$$

and

$$\frac{\partial T}{\partial t} = D(\frac{\partial^2 T}{\partial r^2}) + \frac{kq_P}{\rho C_p} + \frac{q_m}{\rho C_p}$$

(3)

where

$$D = \frac{k}{\rho C_p}$$

These equations are analytically solved to get the two respective temperature profiles. The boundary conditions applied are:

$T_H(0,t)$ = 45 ^0C [Temperature at the centre of the tumour, applied point source temperature]

$T_H(R,t)$ = 37 ^0C [Temperature at the boundary of the tumour, physiological temperature]

And the initial condition used is:

$T_{SS}(r,0)$ = 37 ^0C [Initial temperature of tumour at time t = 0, physiological temperature]

The physiological constant values used in the model from literature [4,9] are:

k = 0.55 $\frac{w}{m * {}^0C}$ [Thermal conductivity of tumour]

ρ = 920 $\frac{kg}{m^3}$ [Density of tumour]

C_P = 3560 $\frac{J}{kg * {}^0C}$ [Heat capacity of tumour]

q_m = 29000 $\frac{w}{m^3}$ [Metabolic heat generation of tumour]

Two models derived analytically are presented, and modelled to approximate the effects of heating the centre of an early stage breast cancer tumour. The models here presume that the ultrasound beam focuses only on the centre of the tumour. As previously stated, the tumour is approximated to be a perfect sphere of uniform density. This means that heat diffuses outwards from the centre for all angles in the sphere. In this sense, it is very similar to modelling the heat diffusion through a slab where distance 'x' is now replaced by a distance 'r' away from the centre as shown in figure 1. Since the sphere is 2 cm in diameter, the model would run for the radius of 1 cm with the ultrasound beam heating the centre to 45 degrees Celsius and the outside surface kept constant at 37 degrees Celsius. Simulation time of 100 seconds of exposure or 1.67 minutes is chosen for the process.

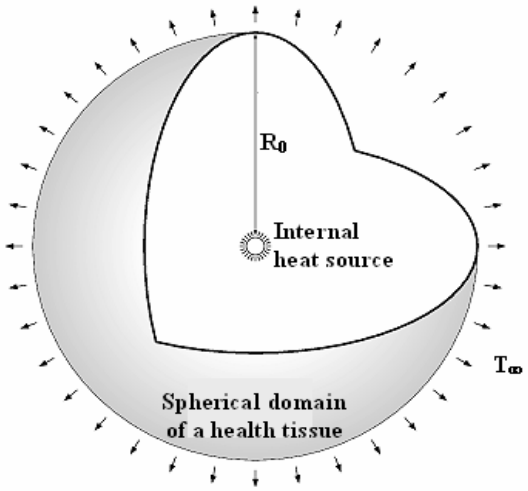

Figure 1: Spherical domain of healthy tissue [10].

In this situation, q_P (the heat perfusion term) is neglected in an attempt to simplify the model. This means that the model can be examined through two scenarios:

1) No consideration of metabolic heat, and
2) Considering the metabolic heat term.

A. *Analytical Solution for Model without External Heat Sources*

Assuming no perfusion of heat from the tumor and blood (q_P), and no metabolic heat released (q_m), the simplified diffusion equation is obtained from equation (3). Hence, the heat transfer of an ultrasound beam on a breast cancer tumor will be modelled

$$\frac{du}{dt} = D\frac{d^2u}{dr^2} + \frac{\cancel{kq_P}}{\cancel{\rho C_P}} + \frac{\cancel{q_m}}{\cancel{\rho C_P}}$$

(4)

where u is temperature (in degrees Celsius) and t is time (in seconds) and r is the distance (in meters).

The complete solution is based on the summation of the homogeneous (U_H) and steady state terms (U_P):

$$U(r,t) = U_H(r,t) + U_P(r)$$

(5)

The boundary conditions are determined to be:

Initial Condition #1: $U(r,0)$ = 37 ^0C

Boundary Condition #1: $U(0,t)$ = 45 ^0C

Boundary Condition #2: $U(R,t)$ = 37 ^0C

These boundary conditions reflect the fact that the temperature of the tumor is initially at physiological body temperature, which is 37 ^0C. The ultrasound laser heats the center of the tumor, at r = 0, to 45 ^0C, which is the first boundary condition. The edge of the

tumor at r = R is modeled to be at body temperature, 37 ^0C .

Solving the steady state term (U_P) at the boundary conditions,

$$\frac{du}{dt} = 0 = \frac{d^2u}{dr^2}; U_P(r,t) = \frac{-8r}{R} + 45$$

(6)

Rescaling to homogeneous initial and boundary conditions:

$$U_H(r,t) = U(r,t) - U_P(r)$$

(7)

Hence, New Initial Condition (IC):

$$U_H(r,0) = 8(-1 + \frac{r}{R})$$

New Boundary Conditions (BC):

$$U_H(0,t) = 0 \; and \; U_H(R,t) = 0$$

Separating variables,

$$U_H(r,t) = \psi(r)G(t)$$

(8)

The solution to equation (8) gives,

$$G = Ce^{-\lambda Dt}$$

(9)

And for cases of λ > 0 (other cases proven to be trivial solutions) the characteristic equation of $\psi(r) = A\cos\sqrt{\lambda}r + B\sin\sqrt{\lambda}r$ is attained. Inputting the boundary conditions yields:

$$\lambda = (\frac{n\pi}{R})^2 \text{ and } \psi(r)B\sin(\frac{n\pi r}{R})$$

(10)

Substituting equations (10) and (9) into equation (8) yields:

$$U_H(r,t) = \sum_{n=0}^{\infty} B \times \sin(\frac{n\pi r}{R}) e^{-(\frac{n\pi}{R})^2 Dt}$$

(11)

Where

$$B = \frac{2}{R}\int_0^R U_H(r,0)\sin(\frac{n\pi r}{R})dr$$

Substituting the new Initial and Boundary conditions into the above equation for B and integrating equation (11) becomes

$$U_H(r,t) = \sum_{n=0}^{\infty} (\frac{-8}{n\pi}) \times \sin(\frac{n\pi r}{R}) e^{-(\frac{n\pi}{R})^2 Dt}$$

(12)

In order to obtain the complete temperature profile, from equations (5), (6) and (12) we obtain,

$$U(r,t) = \frac{-8r}{R} + 45 + \sum_{n=0}^{\infty} (\frac{-8}{n\pi}) \times \sin(\frac{n\pi r}{R}) e^{-(\frac{n\pi}{R})^2 Dt}$$

(13)

B. *Analytical Solution for Model with Addition of Metabolic Heat Term*

Assuming no perfusion of heat from the tumor and blood (q_P), and with an addition of metabolic heat (q_m), the simplified diffusion equation is obtained as in equation (14), where u is temperature (in degrees Celsius) and t is time (in seconds) and r is the distance (in meters):

$$\frac{du}{dt} = D\frac{d^2u}{dr^2} + \frac{\cancel{kq_P}}{\cancel{\rho C_P}} + \frac{q_m}{\rho C_P}$$

(14)

The complete solution is based on the summation of the homogeneous (U_H) and steady state terms (U_P) based on equation (7). Also, the boundary conditions remain the same. Solve the steady state term and putting in the boundary conditions, we obtain

$$\frac{du}{dt} = 0 = \frac{d^2u}{dr^2} + \frac{q_m}{\rho C_P}; \quad \text{Now } D = \frac{k}{\rho C_P}$$

Hence,

$$U_P(r,t) = \frac{-q_m r^2}{2k} + \frac{(-8 + \frac{q_m r^2}{2k})r}{R} + 45 \qquad (15)$$

Considering equation (7) for homogeneous initial and boundary conditions:

New IC: $U_H(r,0) = -8 + \frac{q_m r^2}{2k} - \frac{(-8 + \frac{q_m r^2}{2k})r}{R}$

New BCs: $U_H(0,t) = 0 \; and \; U_H(R,t) = 0$

Following similar steps taken from equations (8) - (11) we obtain,

$$U_H(r,t) = \sum_{n=0}^{\infty} \frac{2}{R}[(\frac{8R}{n\pi})(\cos(n\pi) - 1) + \frac{q_m}{2k}(\frac{-R^3}{n\pi}\cos(n\pi) + \frac{2R^3}{(n\pi)^3}(\cos(n\pi) - 1)) - \frac{R(8 - q_m R^2)}{2kn\pi}\cos(n\pi)] \times \sin(\frac{n\pi r}{R}) e^{-(\frac{n\pi}{R})^2 Dt}$$

(16)

Again we substitute equations (16) and (15) into (7) in order to obtain the complete temperature profile. Hence,

$$U_H(r,t)=\frac{-q_m r^2}{2k}+\frac{(-8+\frac{q_m r^2}{2k})r}{R}+45+\sum_{n=0}^{\infty}\frac{2}{R}[(\frac{8R}{n\pi})(\cos(n\pi)-1)+\frac{q_m}{2k}(\frac{-R^3}{n\pi}\cos(n\pi)+\frac{2R^3}{(n\pi)^3}(\cos(n\pi)-1))-\frac{R(8-q_m R^2)}{2kn\pi}\cos(n\pi)]\times\sin(\frac{n\pi r}{R})e^{-(\frac{n\pi}{R})^2 Dt} \quad (17)$$

The mathematical software MATLAB® (MATrix LABoratory by The Mathworks Inc, USA) was used to compute the temperature distribution at the nodes of a 3-D finite element mesh. Figure 1 shows the schematic geometric diagram of the tissues and heat source used in the computational model.

III. RESULTS AND DISCUUSSION

A. Analytical Solution for Model without External Heat Sources

The first model shows the heating profile of a tumor in an isolated system, which means there are no external factors to consider. Figure 1 shows the diffusion of heat through the tumor if no means of heat loss were present.

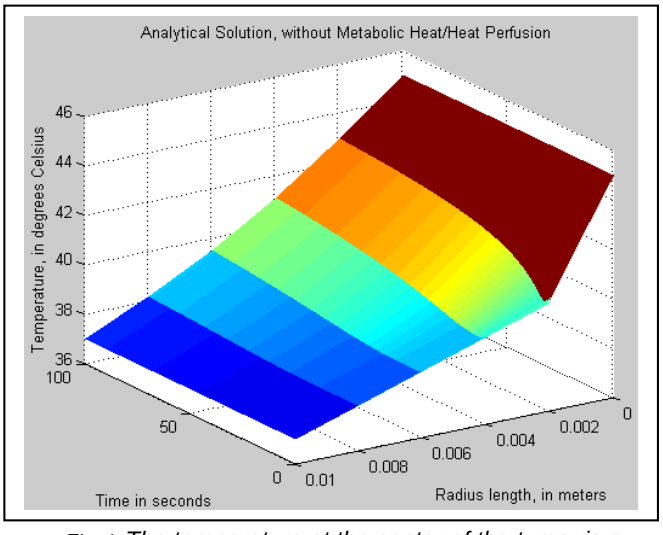

Fig. 1. *The temperature at the center of the tumor is a constant 45 ^0C . With time, the temperature of the tumor gradually increases.*

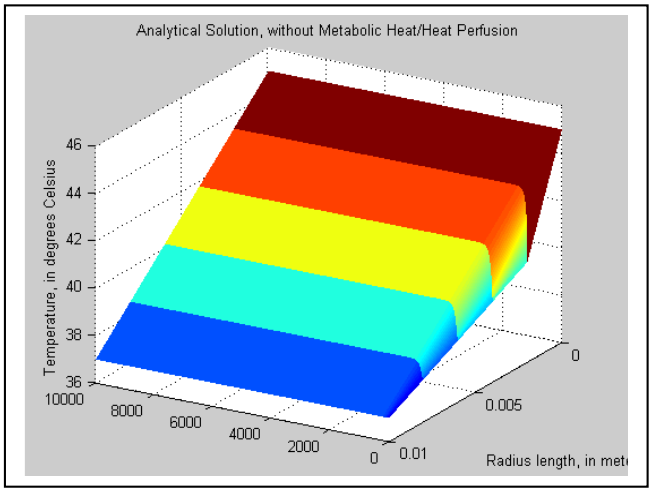

Fig. 2. *Temperature profile for a tumour isolated from the body, for 10000 seconds*

The temperature throughout the tumor is higher than the previous model which is more preferable since a longer time is allotted for the tumor to heat as shown in figure 2.

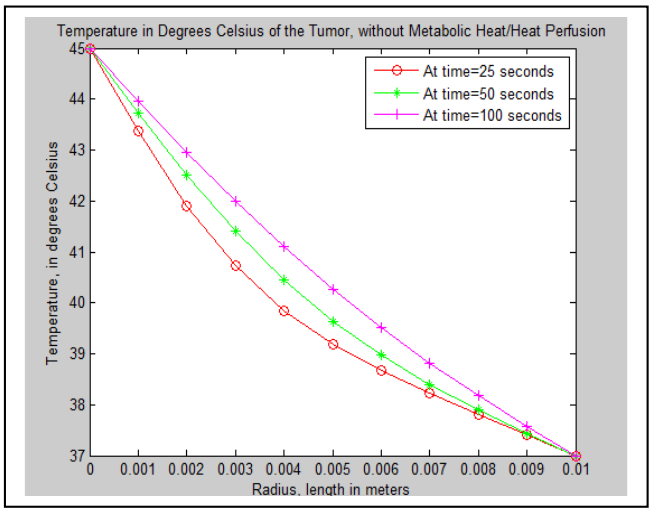

Fig. 3. *Effect of time on the analytical solution.*

Figure 3 confirms that with increasing time, the temperature of the tumor increases.

B. Analytical Solution for Model with Addition of Metabolic Heat Term

The second model is similar to the first but takes into account the metabolic heat generated by the cells themselves. The metabolic heat constant used is $29000\frac{w}{m^3}$ [9]. It is expected that the heat generated by the living tissue would have an additive effect on the external heat generated by ultrasound. The hypothesis would be that the tumor would reach an overall higher temperature and also heat at a faster rate.

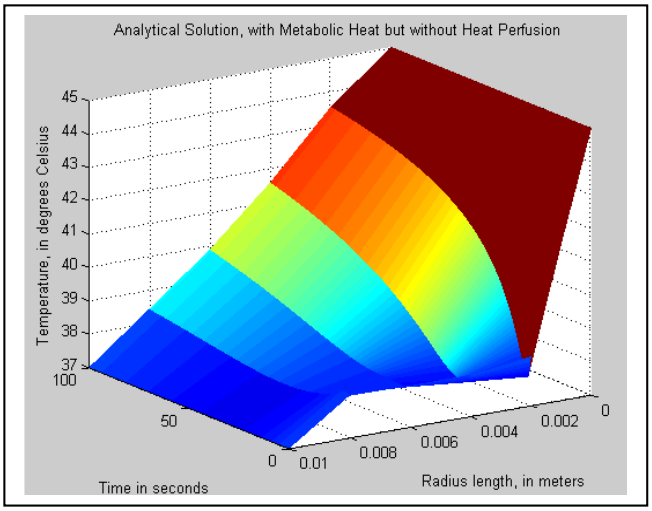

Fig. 4. *Temperature profile for a tumour in the body taking into account metabolic heat generated for 100 seconds.*

The heat source at 45 ${}^{0}C$ heats the tumour to a different gradient as the isolated tumor, but still increases the overall temperature.

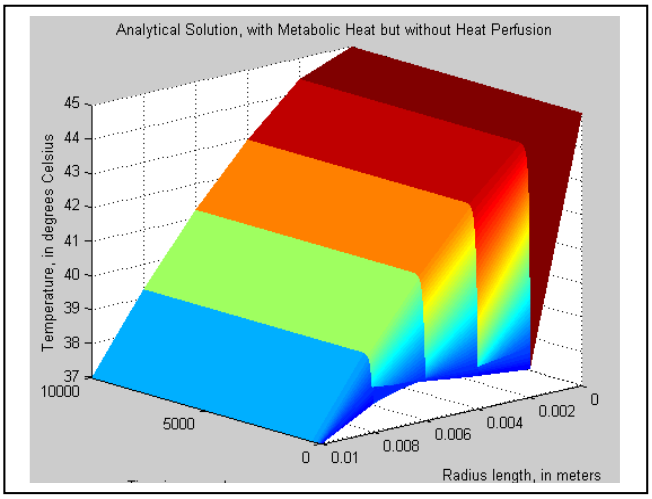

Fig. 5. *Temperature profile for a tumour in the body taking into account metabolic heat generated for 10000 seconds.*

The overall temperature of the tumor increases as treatment time progresses, as observed in the final temperature profile.

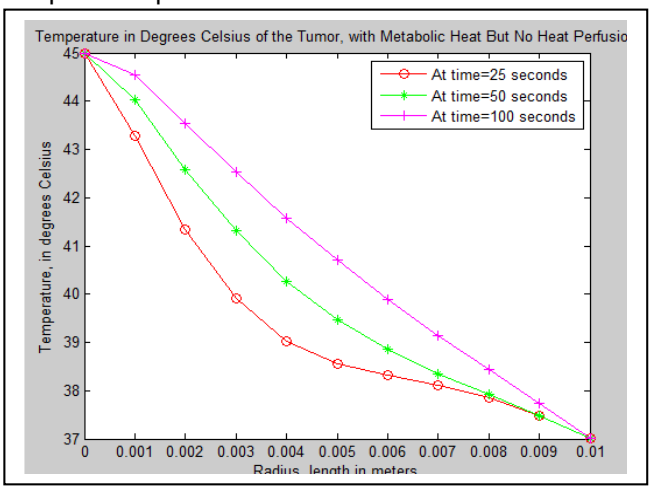

Fig. 6. *Effect of varying exposure times on the analytical solution.*

At time = 100 seconds, it can be seen that the temperature is higher at all points throughout the periphery of the spherical tumor model. Although for lower time, this is not always the case.

Comparing Figures 3 and 6, the most unusual observation from these plots is that with the metabolic heat term introduced into the system, the temperature is lower for shorter exposure periods to the ultrasound. It is originally expected that there will be a uniform shift upwards but this is only seen at the final time point of 100 seconds. Therefore, it is observed that the introduction of metabolic heat affects the effectiveness of the ultrasound beam in some way that the temperature is lower than without the additional heat generation.

IV. RESULTS

Ultrasound presents a new mode in the treatment of cancerous tumours by the use of thermotherapy, resulting in minimal damage to surrounding tissues. Most normal tissues are not damaged during hyperthermia if the temperature remains under 43.9 ${}^{0}C$

However, due to differences in tissue characteristics, higher temperatures may occur in various spots that result in burns, blisters, discomfort, or pain. Ultrasound reduces the damage to surrounding tissue by having a less pronounced effect on less dense tissue.

The presented models show that for a relatively small tumour (2 cm in diameter) and a point heat source set at 45 ${}^{0}C$, only a small part in the interior of the tumour would be damaged and/or destroyed within a period of approximately 100 seconds. However, it is good to note that this is a simplified model that is not taking into

account arterial heat perfusion. The selected heat source temperature is relatively low and to achieve better results, a point heat source at a higher temperature would be more effective at generating sufficient temperature within the tumour. However, this comes at the risk of damaging the surrounding tissue even with the relative safety of ultrasound.

The results of this very simplified model form a basic foundation for a better understanding for the use of ultrasound for thermotherapy treatment and how heat diffusion works in tumours in general. To further our understanding of the effect of ultrasound, more complex and extensive analytical methods including all aspects of heat conduction, perfusion and metabolic heat terms should be considered to form a

more complete picture of the phenomena that occurs in the application of ultrasound.

Two major technical constraints make this mathematical models complicated, the ability to achieve a uniform temperature into the breast tumour, and the ability to precisely monitor the temperatures of both the tumour and the surrounding tissues.

The application of the mathematical technique developed in this study, can be used in the prediction/monitoring of the temperature profile in thermotherapy in the delivery of the appropriate amount of heat to the correct part of the patient's breast, to avoid excessive temperature that may result in surface burns, swelling, bleeding, infection, heart problem or even death. These models have the potential of being developed or applied into a viable alternative to current clinical temperature monitoring device for microwave treatment of breast cancer.

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