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STUDY OF THE BIOHEAT EQUATION WITH A SPHERICAL HEAT SOURCE FOR LOCAL MAGNETIC HYPERTHERMIA

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Abstract. *Hyperthermia is a type of cancer treatment in which cancer cells are exposed to high temperatures (up to 44-45°C). Research has shown that high temperatures can damage and kill cancer cells, by a localized and concentrated heating source. By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors, with minimal injury to normal tissues.*
In addition to in vitro and in vivo studies, computer simulation can be used to understand transport phenomena inside a tumor. In this study a spherical region containing a magnetic particle embedded in a tissue is modeled using the bioheat equation with the Penne's model for the thermal interaction between the tissue and the perfused blood. Analytical techniques are used to solve the bioheat equation with a point heat source of constant density power located as the center of a spherical domain. The point heat source model the heat generated by magnetic particles under the effect of an alternating magnetic field, used in studies of local magnetic hypertermia. Parametric studies of the temperature profiles are carried out to study the effect of different parameters like the heat generation rate, perfusion rate and diameter of the point source on the maximum temperature and on the temperature profile. Some discussion about important parameters research issues in cancer hypertermia are also addressed.

Key words: Hyperthermia; localized heat source; the bioheat *equation.*

NOMENCLATURA

ρ, C_p, k, α : density, specific heat, thermal conductivity and thermal diffusivity of the tissue

ρ_b, C_{pb} : density and specific heat of the blood

$\dot{q}_m$: metabolic heat generation

$\dot{q}_p$: perfusion heat source

ω: perfusion rate (m^3/s of volumetric blood flow per m^3 of tissue)
T_∞ arterial temperature
T, T^*: local tissue temperature and dimensionless local tissue temperature
$\dot{Q}(r)$: point source heat generation
r, r^*: radial coordinate and dimensionless radial coordinate
r_1, R_o: radius of the internal heat source, maximum radius of the domain
t, t^*: time and dimensionless time
$I_{1/2}, K_{1/2}$: modified Bessel functions of order ½

1 – INTRODUCTION

Bioheat transfer processes in living tissues are often influenced by the influence of blood perfusion through the vascular network on the local temperature distribution. When there is a significant difference between the temperature of the blood and the tissue through which it flows, convective heat transport will occur, altering the temperatures of both the blood and the tissue. Perfusion based heat transfer interaction is critical to a number of physiological processes such as thermoregulation and inflammation.

The blood/tissue thermal interaction is a function of several parameters including the rate of perfusion and the vascular anatomy, which vary widely among the different tissues, organs of the body, and pathology. The literature contains an extensive compilation of perfusion rate data for many tissues and organs. The rate of perfusion of blood through different tissues and organs varies depending on factors such as physical activity, physiological stimulus and environmental conditions. Further, many disease processes are characterized by alterations in blood perfusion, and some therapeutic interventions result in either an increase or decrease in blood flow in a target tissue. A good reference for the study of bioheat transfer can be found in the *CRC Handbook of Thermal Engineering, chapter 4.4*(Ed. Frank Kreith, 2000).

Bagaria, and Johnson (Bagaria, and Johnson, 2003, 2005) studied the the bioheat equation numerically and analytically for hyperthermia applications of cancer treatments. The model studies the proper distribution of magnetic particles throughout the tumor could minimize the damage to the surrounding healthy tissue while still maintaining a therapeutic temperature in the tumor. However, this distribution is defined mathematically but is not feasible to control in practical applications. And the analytical solution is complicate and obscure. Rosensweig, (Rosensweig, 2002) present a model for heating magnetic fluid with alternating magnetic field.

In this paper an analytical study is curried out to solve the bioheat equation with a heat source of constant density power located as the center of a spherical domain. The point heat source model the heat generated by magnetic particles under the effect of an alternating magnetic field, used in studies of local magnetic hypertermia. Parametric studies of the temperature profiles are carried out to study the effect of different parameters like the heat generation rate, perfusion rate and diameter of the point source on the maximum temperature and on the temperature profile. Some discussion about important parameters research issues in cancer hypertermia are addressed.

2 - MATHEMATICAL FORMULATION

Pennes model (Pennes, 1948) describes the effects of metabolism and blood perfusion on the energy balance within tissue. Basically, these two effects are incorporated into the standard thermal diffusion equation and the equation is called the bioheat equation. Here, the domain of study will be a spherical domain with a heat source of radius r_1 at the center of the spherical domain of radius R_0 as is shown schematically in Figure 1.

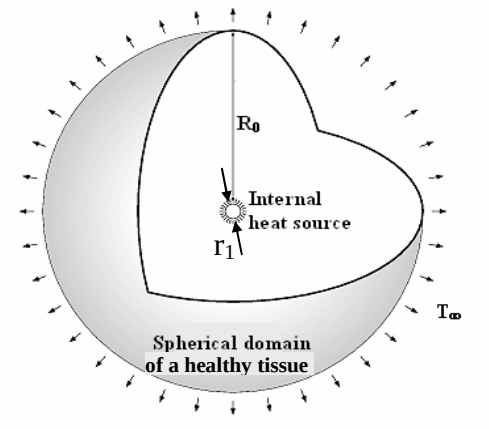

Figure 1 – Schematic of the spherical domain with an internal heat source

The bioheat equation in spherical coordinates with an internal heat generation at the center of the sphere can be written as:

$$\frac{\rho C_p}{k}\frac{\partial T}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right) + \dot{q_p} + \frac{\dot{q_m}}{k} + \frac{\dot{Q}(r)}{k} \tag{1}$$

Where ρ, C_p, k are the density, specific heat and thermal conductivity of the tissue, ρ_b, C_{pb} are density and specific heat of the blood, $\dot{q_m}$ is the metabolic heat generation. Pennes's model for the perfusion heat source is $\dot{q_p} = \frac{\omega\rho_b C_{pb}}{k}(T_\infty - T)$, where ω: is the perfusion rate (m^3/s of volumetric blood flow per m^3 of tissue), T_∞ is the arterial temperature and T is the local tissue temperature. Then, by incorporating the Pennes's model into the diffusion equation (1) yields:

$$\frac{\rho C_p}{k}\frac{\partial T}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right) + \frac{\omega\rho_b C_{pb}}{k}(T_\infty - T) + \frac{\dot{q_m}}{k} + \frac{\dot{Q}(r)}{k} \tag{2}$$

Defining the following dimensionless parameters: $r^* = \frac{r}{R_o}$, $t^* = \frac{\alpha t}{R_o^2}$ and $T^* = \frac{T - T_\infty}{T_\infty}$. Writing equation (2) in terms of these dimensionless parameters, a dimensionless equation is obtained:

$$\frac{1}{r^{*2}}\frac{\partial}{\partial r^*}\left(r^{*2}\frac{\partial T^*}{\partial r^*}\right) - \frac{\partial T^*}{\partial t^*} - \frac{R_o^2\omega\rho_b C_{pb}}{k}T^* = -\frac{\dot{Q}R_o^2}{kT_\infty} - \frac{\dot{q_m}R_o^2}{kT_\infty} \tag{3}$$

By defining the following constants, $Q_o = \frac{kT_\infty}{R_o^2}$ and $C_o = \frac{k}{R_o^2}$ that dimensionalize $\dot{Q}, \dot{q_m}$ and $\omega\rho_b C_{pb}$ as: $Q^* = \frac{\dot{Q}}{Q_o} + \frac{\dot{q_m}}{Q_o}$, $c^* = \frac{\omega\rho_b C_{pb}}{C_o}$, the bioheat equation in dimensionless form can be written as:

$$\frac{1}{r^{*2}}\frac{\partial}{\partial r^*}\left(r^{*2}\frac{\partial T^*}{\partial r^*}\right) - \frac{\partial T^*}{\partial t^*} - c^* T^* = -Q^*(r^*) \tag{4}$$

With the following initial condition, $T^*(r^*, t=0) = 0$ and the following boundary conditions: the temperature must remain finite at the center $T^*(0, t^*) = \textit{finite}$ and the temperature at the external spherical surface is maintained at T_∞, so the dimensionless temperature $T^*(r^*=1, t) = 0$

3 – ANALYTICAL SOLUTION

To obtain an analytical solution, let split the dimensionless heat generation term $Q^*(r)$ into a constant heat generation due to metabolism q_m^* and a constant heat source of radius r_1 at the center $q_p^{c*}(r)$

$$Q_{(r)}^* = q_m^* + q_p^{c*}(r)$$

Then

$$\frac{1}{r^{*2}}\frac{\partial}{\partial r^*}\left(r^{*2}\frac{\partial T^*}{\partial r^*}\right) - \frac{\partial T^*}{\partial t^*} - cT^* = -q_m^* - q_p^{c*}(r) \tag{5}$$

Now, let $T^* = T_1(r,t) + T_2(r)$ and for convenience let drop the superscript *

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T_1}{\partial r}\right) - \frac{\partial T_1}{\partial t} - cT_1 = -q_{p(r)}^c \tag{6}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T_2}{\partial r}\right) - cT_2 = -q_m \tag{7}$$

Subject to the following boundary conditions:

$$T_1(r=1,t) = 0 \text{ and } \quad T_1(r=0,t) = \textit{finite} \tag{8}$$

$$T_2(r=1) = 0 \quad \text{and} \quad T_2(r=0) = \textit{finite} \tag{9}$$

And the following initial condition:

$$T_1(r,0) = -T_2(r) \quad \text{since} \quad T^*(r,0) = T_1(r,0) + T_2(r) = 0 \tag{10}$$

Now, let $T_1(r,t) = e^{-ct}U(r,t)$ and substitute into equation (6)

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial U}{\partial r}\right) - \frac{\partial U}{\partial t} = -q_p^c(r)e^{ct} = g(r,t) \tag{11}$$

Where the source term is now a function of *r* and *t*, $g(r,t) = -q_p^c(r)e^{ct}$. Then, the boundary conditions in terms of *U* yields:

$$U(r=1,t) = 0 \text{ and } \quad U(r=0,t) = \textit{finite} \tag{12}$$

And the initial condition becomes:

$$U(r,t=0) = -T_2(r) \tag{13}$$

Then, equation (7) has to be solved subject to boundary conditions (9) and equation (11) subject to boundary conditions (12) and initial condition (13). With the following change of variables for $T_2(r) = \frac{H(r)}{\sqrt{r}}$, equation (7) becomes a modified Bessel equation in terms of *H* and the solution is obtained in terms of modified Bessel functions (see Appendix A)

$$T_2(r) = \frac{q_m}{c}\left(1 - \frac{I_{1/2}\left(r\sqrt{c}\right)}{\sqrt{r}I_{1/2}\left(\sqrt{c}\right)}\right) \tag{14}$$

The solution equation (11) for U is obtained using Green functions with an initial condition given by

$$U(r,0) = -T_2(r) = -\frac{q_m}{c}\left(1 - \frac{I_{1/2}\left(r\sqrt{c}\right)}{\sqrt{r}I_{1/2}\left(\sqrt{c}\right)}\right) \tag{15}$$

A spherical heat source of radius r_1 placed at the center of the spherical domain of integration

$$g(r,t) = g_p^c e^{ct}\frac{1}{4\pi r^2}\delta(r - r_1)$$

$$\begin{aligned} U(r,t) = {} & \frac{2}{r}\sum_{m=1}^{\infty} e^{-\beta_m^2 t}\sin\left(\beta_m r\right)\int_0^1 r'\sin\left(\beta_m r'\right)\left(-T_2(r')\right)dr' + \\ & + \frac{1}{2\pi r_1 r}\sum_{m=1}^{\infty} e^{-\beta_m^2 t}\sin\left(\beta_m r\right)\sin\left(\beta_m r_1\right)\int_{\tau=0}^{t} e^{\beta_m^2\tau} g_p^c e^{c\tau} d\tau \end{aligned} \tag{16}$$

The integral $\int_{\tau=0}^{t} e^{\left(\beta_m^2+c\right)\tau} g_p^c d\tau$ can be integrated analytically for a constant intensity heat generation g_p^c

$$\int_{\tau=0}^{t} e^{\left(\beta_m^2+c\right)\tau} g_p^c d\tau = \left[\frac{e^{\left(\beta_m^2+c\right)\tau} g_p^c}{\beta_m^2+c}\right]_0^t = \frac{e^{\left(\beta_m^2+c\right)t}-1}{\beta_m^2+c} g_p^c$$

Going back to $T_1 = Ue^{-ct}$ with $\beta_m = m\pi$, $T_1(r,t)$ takes the form

$$T_1(r,t) = \frac{2}{r}\sum_{m=1}^{\infty} e^{-\left(\beta_m^2+c\right)t} \sin\left(\beta_m r\right) \int_0^1 r' \sin\left(\beta_m r'\right)\left(-T_{2(r')}\right) dr' + \frac{g_p^c}{2\pi r_1 r}\sum_{m=1}^{\infty} \sin\left(\beta_m r\right)\sin\left(\beta_m r_1\right)\left[\frac{1-e^{\left(\beta_m^2+c\right)t}}{\beta_m^2+c}\right] \quad (17)$$

The integral $\int_0^1 r' \sin\left(\beta_m r'\right)\left(-T_2(r')\right) dr'$ can be evaluated numerically. The final solution for T^* is $T^*=T_1(r,t)+T_2(r)$

$$T^*(r,t) = \frac{2}{r}\frac{q_m}{c}\sum_{m=1}^{\infty} e^{-\left(\beta_m^2+c\right)t} \sin\left(\beta_m r\right) \int_0^1 r' \sin\left(\beta_m r'\right)\left(\frac{I_{1/2}\left(r'\sqrt{c}\right)}{\sqrt{r'}I_{1/2}\left(\sqrt{c}\right)} - 1\right) dr' + \frac{q_m}{c}\left(1 - \frac{I_{1/2}\left(r\sqrt{c}\right)}{\sqrt{r}\, I_{1/2}\left(\sqrt{c}\right)}\right) + \frac{g_p^c}{2\pi}\sum_{m=1}^{\infty} \frac{\sin\left(\beta_m r\right)}{\beta_m r}\frac{\sin\left(\beta_m r_1\right)}{\beta_m r_1}\left[\frac{1-e^{-\beta_m^2 t\left(1+\frac{c}{\beta_m^2}\right)}}{1+\frac{c}{\beta_m^2}}\right] \quad (18)$$

Where $\beta_m = m\pi$, $m = 1, 2, 3, \ldots\ldots\ldots\infty$

And from the definition of the dimensionless temperature, $T^* = \frac{T - T_\infty}{T_\infty}$, the temperature T is obtained as $T = T^* T_\infty + T_\infty$

5 - RESULTS AND DISCUSSION

Here, some typical values are assumed for the tissue thermal properties, the metabolic heat generation, the perfusion rate and a radius of a spherical domain under study.

$$k = 0.5\frac{W}{m°C};\ \rho_b = 1000\frac{kg}{m^3};\ C_p = 3600\frac{J}{kg°C};\ T_\infty = 37°C;\ \dot{q}_m = 700\frac{W}{m^3},\ w = 0.0005\frac{1}{s};\ R_o = 0.01m$$

The radius of the internal heat source is r_1= 0.00001 m. With these values, $Q_o = \frac{kT_\infty}{R_o^2}$ and $C_o = k/R_0^2$ are calculated to dimensionalize $\dot{q}_m$ and $c = w\rho_b C_{pb}$

$$Q_o = \frac{kT_\infty}{R_o^2} = \frac{0.5\frac{W}{m°C}\times 37°C}{(0.01m)^2}185000\frac{W}{m^3};\ q_m^* = \frac{\dot{q}_m}{Q_o} = \frac{700W/m^3}{185000W/m^3} = 3.78.10^{-3}; c^* = \frac{c}{C_o} = \frac{w\rho_b C_{pb}}{k/R_0^2} = 0.36$$

The parameter $\frac{\alpha t}{R_0^2}$ dimensionalize the time t

$$t^* = \frac{\alpha t}{R_0^2} = \frac{k}{\rho C_p R_o^2}t = \frac{0.5\frac{W}{m°C}}{1000\frac{kg}{m^3}\times 3600\frac{J}{kg°C}\times(0.01m)^2}1.39.10^{-3}t\frac{1}{s}$$

To evaluate equation (18), an analysis of order of magnitude is performed first. The first term of equation (18) goes to zero when time goes to infinity. Thus, $T_2(r)$ represents the steady state temperature profile due to a constant metabolic heat generation. Assuming only metabolic heat generation, the maximum temperature will occur at the center of the spherical domain at the steady state. The temperature rise due to typical values of metabolic heat generation is negligible compared with the temperature rise due to the heat source that have to be generated by the magnetic particles, in hyperthermia applications. Then, neglecting the first two terms in equation (18), the temperature profile generated by the heat source of radius r_1 at the center of the spherical domain of radius R_0 will be discussed now.

Figure 2 shows the temperature profiles generated by an internal heat source at the center of the sphere of $g_p^c = 1000W/m^3$. The maximum temperature occurs at the center and is approximately 55ºC. The steady state temperature distribution is shown and it can be seen the temperature gradients at the center are very steep to be able to diffuse the heat generated. Since the conductivity of the tissue is low and the cross sectional area in the region close to the heat source is also small, from Fourier law of conduction the temperature gradients have to be high. As the radius is increasing, the heat fluxes are reducing and heat can be diffusive with lower gradients. This implies that in the region next to the heat source, a very steep temperature profile can be maintained for a long time generating higher temperature in a very small region and lower temperatures at a relatively short distance from the heat source, without affecting healthy cells. This is very important in hyperthermia treatments, since is desirable to minimize secondary effects. From parametric studies, the steady state profile is reached in a very short time (much less than one second). At a distant of 0.1 mm the temperature is less than 39 °C. As can be seen, the higher temperatures are concentrated to a short distance from the heat source.

Figure 3 shows the temperature profile for a radius of the internal heat source of r_1=0.0001 m. For the same volumetric heat generation $g_p^c = 1000W/m^3$ the heat power is much higher since the volume increase as the cubic of the radius but the temperatures generated are lower because heat can diffuse easier in this case..

Figure 4 shows the temperature profiles for a radius of the internal heat source of r_1=0.0001 m. as in Figure 3 but a volumetric heat generation of $g_p^c = 7000W/m^3$. It can be seen that the temperature penetrates further into the domain.

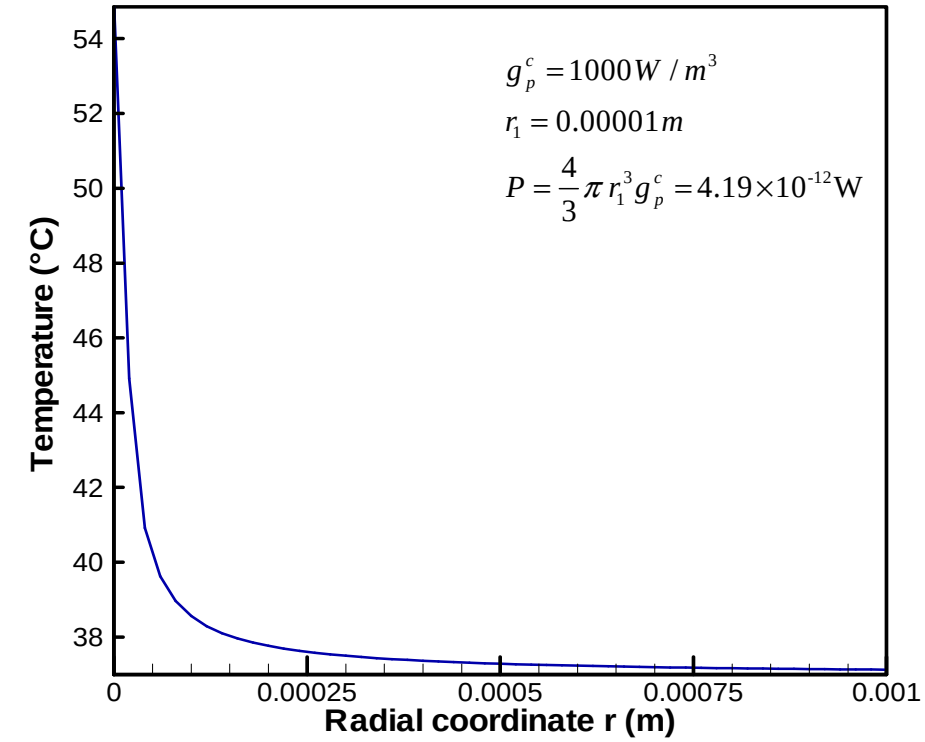

Figure 2 – Steady state temperature profile for r_1=0.00001 m

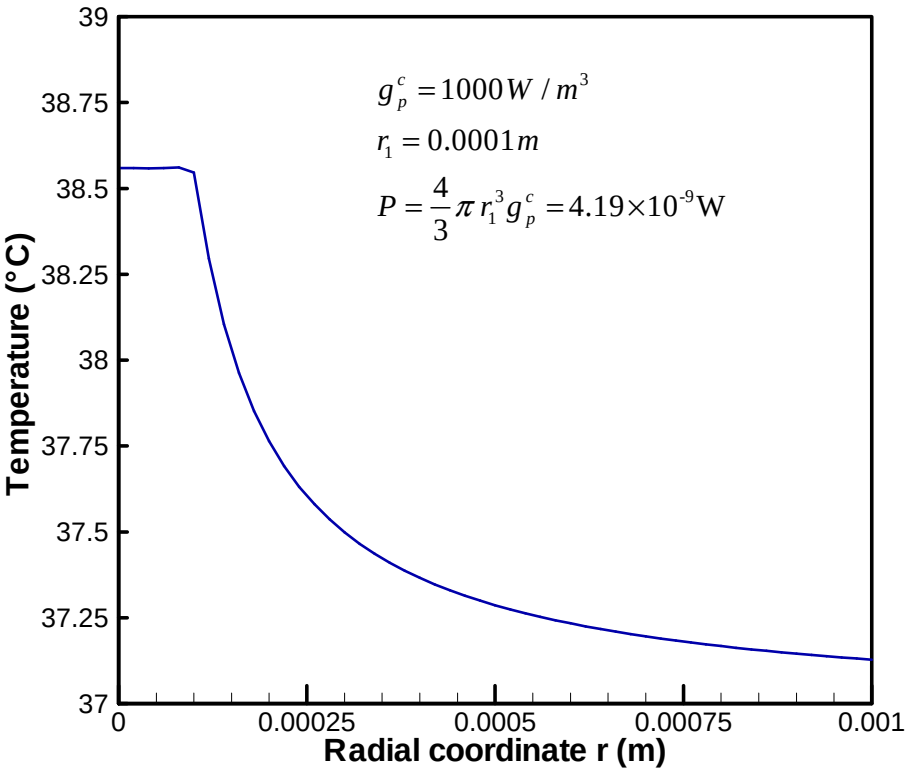

Figure 3 – Steady state temperature profile for r_1=0.0001 m

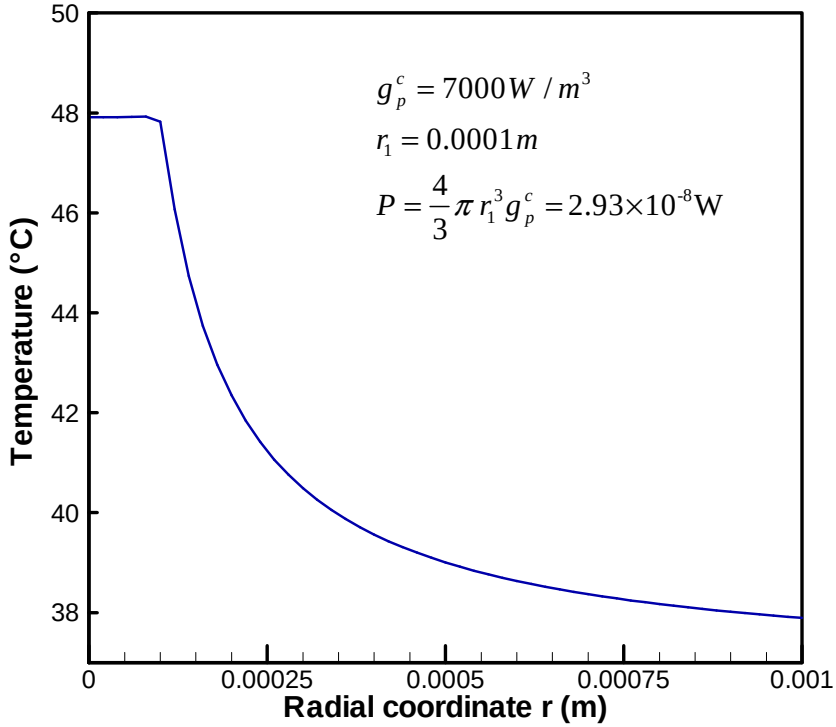

Figure 4 – Steady state temperature profile for r_1=0.0001 m and g_p^c =7000 W/m^3

Finally, from the analytical solution (18), the effect of the perfusion rate is quantified by the term $\frac{c}{\beta_m^2}$. For typical values of *c* in the order of 0.36, c/π^2 is small and the effect of perfusion can be neglected for hyperthermia applications.

6 - CONCLUSIONS

An analytical study of the bioheat equation has been carried out. An analytical solution was obtained for the case of metabolic heat generation in a spherical domain and a concentrated heat source at the center of the sphere. From parametric studies, metabolic heat generation can be neglected because the temperature raise that will generate is small compared with the typical temperature increase generated in hyperthermia applications of cancer treatments. Also, the effect of the perfusion rate is not significant. For very concentrated heat sources, the temperatures gradients are very high and higher temperatures are generated in a small region close to the heat source. A short distance from the source, temperatures can be maintained practically at a tissue temperature without affecting healthy cells. If the size of the heat source increases, the heat diffuses easier and the temperature profile penetrate farther into the healthy cells.

7 - ACKNOWLEDGMENT

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8 - REFERENCES

Kreith F., Timmerhaus K., Lior N., Shaw H., Shah R.K., Bell K. J., *The CRC Handbook of Thermal Engineering.* Ed. Frank Kreith, Boca Raton: CRC Press LLC, 2000

H. G. Bagaria and D. T. Johnson, "Transient solution to the bioheat equation and optimization for magnetic fluid hyperthermia," International Journal of Hyperthermia, vol. 21, pp. 57-75, 2005.

Bagaria, H. and Johnson, D.T., “Analytical and Numerical Solution to a Concentric Sphere Model and Optimization for Magnetic Fluid Hyperthermia Treatment.” International Journal of Hyperthermia 21.1 (2005) 57-75.

Bagaria, H. and Johnson, D.T. “Numerical Solution to the Magnetic Fluid Hyperthermia Heating of Particles Absorbed on a Cell Wall.” Proceedings of the 2003 AIChE Conference, San Francisco, CA.

National Cancer Institute. “Hyperthermia in Cancer Treatment: Questions and Answers.” www.nci.nih.gov.

Rosensweig, R. E. "Heating magnetic fluid with alternating magnetic field," Journal of Magnetism and Magnetic Materials, vol. 252, pp. 370-374, 2002.

Pennes, H. H. "Analysis of tissue and arterial blood temperatures in the resting human forearm," Journal of Applied Physiology, vol. 1, pp. 93-122, 1948.

APENDIX A

To solve equation (A1), given below

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T_2}{\partial r}\right)-cT_2=-q_m \qquad \text{(A1)}$$

The following change of variable $T_2=\frac{H_{(r)}}{\sqrt{r}}$ is made. Then, equation (A1) transforms to

$$\frac{dT_2}{dr}=r^{-1/2}H'-\frac{1}{2}Hr^{-3/2}$$

$$\frac{1}{r^2}\frac{d}{dr}\left[r^2\left(r^{-1/2}H'-\frac{1}{2}Hr^{-3/2}\right)\right]-cr^{-1/2}H=-q_m$$

Multiplying by r^2 and doing $q_m=0$ we obtained the corresponding homogeneous equation.

$$\frac{d}{dr}\left(r^{3/2}H'-\frac{1}{2}Hr^{1/2}\right)-cr^{3/2}H=0$$

By expanding

$$\frac{3}{2}r^{1/2}H'+r^{3/2}H''-\frac{1}{4}Hr^{-1/2}-\frac{1}{2}H'r^{1/2}-cr^{3/2}H=0$$

Multiplying by $r^{1/2}$

$$r^2H''+rH'-\left[cr^2-\left(\frac{1}{2}\right)^2\right]H=0$$

This is the *modified Bessel equation of order ½.* The solution is obtained in terms of the modified Bessel functions $I_{1/2}, K_{1/2}$

$$H=B_1I_{1/2}+B_2K_{1/2}$$

To satisfy the condition that *H* has to be finite B_2=0. Then

$$T_2(r)=B_1\frac{I_{1/2}(r\sqrt{c})}{\sqrt{r}}+\text{Particular solution}$$

If q_m is constant, then the particular solution is

$$T_p=\frac{q_m}{c}$$

Then

$$T_2(r)=B_1\frac{I_{1/2}(r\sqrt{c})}{\sqrt{r}}+\frac{q_m}{c}$$

B_1 is found from the condition

$T_2(r)\big|_{r=1}=0$, which imply that $B_1=-\dfrac{q_m}{cI_{1/2}(\sqrt{c})}$ and the solution for T_2 is

$$T_2(r)=\frac{q_m}{c}\left(1-\frac{I_{1/2}\left(r\sqrt{c}\right)}{\sqrt{r}I_{1/2}\left(\sqrt{c}\right)}\right)$$