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FINITE ELEMENT ANALYSIS OF ULTRASOUND THERMAL DOSE IN SHRINKAGE TUMORS INSIDE HUMAN BODY

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ABSTRACT

In this work the thermal behavior of malignant and healthy human tissue while exposing to ultrasonic waves was studied. Some stand-alone heat therapy is described numerically using Pennes equation which was solved using three level time step procedure to avoid iteration. The efficient procedure of solving the equations by avoiding time consuming procedure of iteration was combined with band solver matrix solution enhanced the program efficiency (i.e. reduce the time of calculation and the size of the program*)* . The temperature distribution was obtained first from which the thermal dose required to shrink a tumor was calculated using well-known thermal dose equations and then the zone that had been necroses was obtained where an effective procedure is proposed to shrink the cancer cells that may exist in certain human tissues. The controlling of the heat dose is the main factor in determining the affected zone by chooses a suitable acoustic window, power and time. The suitable heat can be generated with a human body so as to kill the cancer cells where they may exist. Cancelling the heat source, the temperature of the skin was obtained numerically which was found with good agreement with real skin temperature.

Key words. Hyperthermia, ultrasonic wave, cancer, heat transfer, finite element method

التحليل باستخدام طريقة العناصر المحددة للجرعة الحرارية المتولدة لقتل الورم داخل جسم الانسان من الامواج فوق الصوتيه

الخلاصة :

تم استخدام طريقة العناصر المحددة لوصف السلوك الحراري من نسيج البشري العادي ولنسيج الذي يحتوي على ورم سرطاني خلال التعرض للامواج فوق الصوتيه . تم وصف عملية العلاج الحراري بشكل رقمي باستخدام معادلة بنسن والتي حلت باستخدام طريقة الزمن للمستويات الثلاث لتجنب الحلل التكراي ، وباستخدام هذا الحل الكفوء تم اختصار زمن الوصول الى النتائج والذي حسن كفاءة البرنامج في البداية .تم استنباط توزيع درجات الحرارة ومنها تم استخراج الجرعة الحراية الازمة لقتل الخلاليا السرطانية باستخدام المعادلة المعروفة للجرعة الحرارية وبعدها تم معرفة المنطقة التي تعرضت للضرر الحراري . ان السيطرة على كمية الحرارة المتولدة هو العامل الرئيسي فى ايجاد المنطقة المتأثرة وذلك باختيار حجم مناسب للنافذة الصوتية والقدرة وزمن التعرض . ان كمية الحرارة المناسبة يمكن توليدها فى جسم الانسان لقتل الخلايا السرطانية . ان الغاء المصدر الحرارى فى البرنامج المستخدم يؤدى الى استخراج توزيع درجات الحرارة الطبيعى فى الجسم وهذا ماتم استخراجة حيث لوحظ تطابق بين درجة حرارة الجلد الطبيعى والنتائج المستخلصة من البرنامج المستخدم.

1.INTRODUCTION

A number of different energy sources are used to deliver thermal energy including laser light, microwave and Ultrasonic [Fry,1954.Hunt,1991]. By concentrating the ultrasonic energy, it is possible to selectively heat tumors and protect healthy tissues. The heat dose must be used wisely, too little heat may not kill the cancer cells. However, if too much heat misses the tumor target, the skin or the healthy tissue could be burned.

This paper focuses on this subject by using an outer ultrasonic source to deliver heat into deep tissues where cancer cell may exist. The finite element method is used due to its flexibility in dealing with severe thermal gradient and mesh concentration ability knowing that it is one of the most suitable methods that well describes the thermal behaviors of living cells with its flexibility in dealing with different thermal properties of human cells. The temperature distribution is obtained first from which the thermal dose required to shrink a tumor is calculated using a well-known thermal dose equation and then the zone that had been necrosed by the induced heat is obtained. It is useful to show some previous studies related to the present research.[Sibille,1993]

David M. Brizel , Sean P . Scully, John M . Harrelson[1996]. The adverse prognostic impact of tumor hypoxia has been demonstrated in human malignancy. they report the effects of radiotherapy and hyperthermia (HT) on soft tissue sarcoma oxygenation and the relationship between treatment- induced changes in oxygenation and clinical treatment outcome . Patients receiving preoperative radiotherapy and HT underwent tumor oxygenation measurement pretreatment after the start of radiation /pre-HT and one day after the first HT treatment. The magnitude of improvement in tumor oxygenation after the first HT fraction relative to pretreatment baseline was positively correlated with the amount of necrosis seen in the resection specimen.

Over ahundred years ago, doctors first noticed that high heat, such as that resulting from afever, killed cancer cells and shrank tumors.Today hyperthermia is used as an adjunct to radiation therapy and chemotherapy[Van,2002.Wust,2002] .Hyperthermia treatment of cancer requires directing acarefully controlled dose of heat to the cancerous tumor and surrounding boy tissue.Focused external heating is currently the most preferable method of heating tumors because energy can be localized to the target volume while surrounding healthy tissue is preserved ; in addition to that, it is the most preferable treatment by both patients and doctors.

John D. Hazle , R. Jason Stafford, Roger E. Price[2002] investigated the use of magnetic resonance- guided focused ultrasound therapy as anoninvasive alternative to surgery in the local control of soft- tissue tumors by ablating prescribed volumes of rabbit tumors and comparing with ablation of normal tissue volumes. Excellent correlation was observed between prescribed treatment volumes , thermal dosimetry ,post- treatment verification , and histopathology. Multifocal ablations of tumors in rabbits at depths of up to 2.5 cm resulted in complete ablation of the prescribed treatment volume. Techniques developed for treatments in homogeneous tissue volumes are applicable in the more complicated tumor environment if temperature feedback is available to modify treatment delivery parameters.

A thermal lesion determination scheme is proposed to offer an easy but useful guideline to precisely heat the selected deep-seated tumors[He-lo2003]. The key factor is only affected by blood perfusion rate while the heating volume is large enough. This strategy provides a simple implementation to perform "on-line feedback" control in ultrasound thermal therapy.

Heman I. Vargas, William C, Dooley , Robert[2003], investigated the tumor ablation as amean of treating breast cancer. Mictowave energy is promising because it can preferentially heat high-water content breast carcinomas ,compard to adipose and glandular tissues. This is a prospective, multicenter , nonrandomized dose- escalation study of microwave treatment .thermal dose was measured as (1) thermal equivalent minutes (cumulative equivalent minutes; CEM) of treatment relative to a temperature of 43 c and (2) peak tumor temperature. Microwaves were guided by an antenna -temperature sensor placed percutaneously into the tumor do. Thermotherapy causes tumor and can be performed safely with minimal morbidity. The degree of tumor necrosis is a function of the thermal dose. Future studies will evaluate the impact of high doses of thermotherapy on margin status and complete tumor ablation.

Donald E .Thrall, Susan M .LaRue ,Daohai[2005] tested prospective delivery of higher thermal dose associated with longer tumor control duration. Thermal dose is directly related to local duration in irradiated canine sarcomas. Longer heating being associated with shorter local tumor control was unexpected. Howere, the effect of thermal dose on tumor control was stronger than forheating duration . The heating duration effect is possibly mediated through delirious effects on tumor oxygenation .These results are the first to show the value of prospectively controlled thermal dose in achieving local tumor control with thermoradiotherapy , and they establish a paradigm for prescribing thermoradiotherapy and writing athermal prescription.

Kullervo Hynynen[2006] , retrospectively evaluate magnetic resonance (MR) imaging -based treatments of uterine leiomyomas ,while the thermal dose estimates were shown to have a clear relationship with the dose estimates times as large for area that reach 240 and 18 minute threshold dose values.

Manfred Johannsen, Uwe Gneveckow , Bur.Cho[2006] investigated the feasibility of thermotherapy using patients with locally recurrent prostate cancer and to calculation of the three-dimensional temperature distribution. Ten patients with locally recurrent prostate cancer to entered into aprospective. Patients received six thermal using an alternating magnetic field applicator .The heating technique using magnetic nanoparticle temperature were achieved in the prostates at 25% of significant potential for higher temperature .A noninvaed could be developed , which may be used for thermal dose.

2. THOREY

2.1. Partial differential equation

Based on the well known Pennes bio-heat equation [Vaughan,1994.Pennes,1948] and due to symmetrical nature of the problem an axis-symmetry bio-heat equation is used[Murt,2006]

$$\rho\, c\frac{\partial T}{\partial t} = \frac{1}{r}\left[k\frac{\partial}{\partial r}(r\frac{\partial T}{\partial r})\right] + k\ \frac{\partial^2 T}{\partial z^2} + Wc_b(T_B - T) + \dot{Q} + Q_m \qquad \textbf{(1)}$$

This equation has to be solved to determine temperature distribution through the human tissue. The basal temperature is assumed to be 37 ◦ C. The heat generation is produce by using an ultrasound focused source,see table (1). Tabel 1 shows thermal properties of tissue and enviermental conditions.

2.2 Ultrasound wave as heat source:

The heat generation is result from ultrasound heat source. The ultrasound wave targeted region diameter is d_t. The ultrasound wave is assumed to propagate in straight line and they are diverged beyond Z_t , the diameter of the ultrasound window is then can be modeled as shown in Fig (1).

Then the the variation of acoustic diameter with depth can be written as:

$$d(z) = d_t + (d_f - d_t)\frac{|z - z_t|}{z_t} \qquad \textbf{(2)}$$

The deposition of the ultrasonic intensity at each depth is considered to be distributed symmetrically along the z-axis assuming that the ultrasonic power intensity in not too large to cause wave distortions and all the attenuated energy is absorb by the tissue. The acoustic attenuation coefficient depends on the driving frequency and is approximately 5Np m^{-1} at 1 MHz and 10 Np m^{-1} at 2MHz [Spareto.1984], a conditioned case is studied where the absorb power density (Apd) at the focal depth is equal to 15W cm^{-3} . Then the heat generation can be calculated from [Foster,1979]:

$$\dot{Q} = Apd(z) = Apd(z_t)\frac{d^2(z_t)}{d^2(z)}e^{-2\mu(z-z_t)} \qquad \textbf{(3)}$$

Which is referred to heat generation per unit volume at specified depth.[Lewis,1996].

2.3 Finite element formulation

The space wise discretization of axis-symmetry bio-heat equation subject to the above boundary condition can be accomplished using Galerkin method .The volume of interest Ω is divided into a number of elements, Ω^e ,with usual shape function N_i associated with each node, the unknown function T is approximated through the solution domain at any time by

$$T = \sum N_i(r,z,t)\, T_i(t) \qquad \textbf{(4)}$$

Where $T_i(t)$ are the nodal parameters. Substitution of the above equation into bio-heat equation and the application of Galerkin method results in a system of ordinary differential equations of the form [Sapareto,1984]

$$[C]\,\dot{\vec{T}} + [K]\,\vec{T} + [F] = 0 \qquad \textbf{(5)}$$

Where $\dot{\vec{T}} = \begin{Bmatrix} \frac{\partial T_1}{\partial t} \\ \frac{\partial T_2}{\partial t} \\ \\ \\ \frac{\partial T_p}{\partial t} \end{Bmatrix}$, $\vec{T} = \begin{Bmatrix} T_1 \\ T_2 \\ .. \\ .. \\ T_p \end{Bmatrix}$ and $[F] = \begin{Bmatrix} F_1 \\ F_2 \\ .. \\ F_p \end{Bmatrix}$ and p is the total no. of node

The typical matrix elements are

$$K_{ij} = \sum \int_{\Omega^e} (k(\frac{\partial N_i}{\partial r}\frac{\partial N_j}{\partial r}) + k(\frac{\partial N_i}{\partial z}\frac{\partial N_j}{\partial z}))d\Omega + \sum \int_{\Omega^e} (N_i W c_b)d\Omega + \sum \int_{\Gamma^e} N_i h d\Gamma \qquad (6)$$

$$C_{ij} = \sum \int_{\Omega^e} \rho \ \ c \ N_i N_j d\Omega \qquad (7)$$

$$F_i = -\sum \int_{\Gamma^e} N_i h T_\infty)d\Gamma - \sum \int_{\Omega^e} N_i(\dot{Q} + Q_m + W c_b T_B)d\Omega \qquad (8)$$

In the above, the summation are taken over the contribution of each element, Ω^e ,in the element volume and Γ^e refers only to the element with external boundary on which surface condition is applied. To avoid iteration at each time step, the unconditionally stable three level scheme proposed by Lees, is used here R.W .Lewis [R.W.Lewis2006]. Using the shape function which normalize to time interval Δt , the result is in standard shape function , then the application of weighted residual theory to equation(8) results is in matrix form of

$$\left(\frac{3[C_n]}{2\Delta t} + [K_n]\right)\bar{T}_{n+1} = -\left([K_n]\bar{T}_n + [K_n]\bar{T}_{n-1} - \frac{3}{2\Delta t}[C_n]\bar{T}_{n-1} + 3\bar{F}\right) \qquad (9)$$

In this solution a well-known method suggested by reference [R.W.Lewis2006] is used to avoid iteration with each time step. The values of matrices at the intermediate time will be sufficient to solve the simultaneous equations at each time step. The values of the temperature at the end of the total three level will be replaced by the intermediate values for the next time step and so on and an easily two starting values of the temperature distribution can assumed to start the solution of eq (12). The efficient procedure of solving the equations by avoiding time consuming procedure of iteration is combined with band solver matrix solution will dramatically reduce the time of calculation and the size of the program.

2.4 Thermal dose calculations

The thermal dose calculation in term of equivalent minutes at 43 ° C is used to estimate the necrosed tissue volume, and is calculated using the following equation [Chato,1990.Damianou,1995]

$$TD = \int_{t_o}^{t_f} S^{(T-43)}dt \qquad (10)$$

Where

S=2 for T ≥ 43 ° C **(10 a)**

And S=4 for $37^\circ C < T < 43^\circ C$ **(10 b)**

The thermal dose value required for the total necrosis ranges from 25 to 240 minutes for brain to muscle tissues [Dewey,1994. Arkin,1994] the last one is taken in this work as a necroses limits since we are dealing with cancer combined with muscles tissue. It is worthwhile to mention that the thermal dose is calculated through the hole period of temperature exposed (i.e. as long as temperature is greater that $42^\circ C$). Note that that the thermal dose for temperature < $42^\circ C$ is very small, this will significantly reduce the time of calculation. Fig (2) shown the block diagram of program.

2.5 Thermal properties of tissue and perfusion rate

Many references had well established the thermal properties of human tissue which are used in this work, see table 2

Fig 3 shows the general structure of skin, the most amazing property is that the perfusion rate of tumor (cancer cell) is less than that of the surrounding healthy tissue, this factor plays an important rule in dissipation heat then the dissipation of heat within cancer cell will be less than that of the surrounding healthy tissue. Thermally this means that the tumor will reach high temperature and may be kept around there for time longer than that of the healthy tissue which means high tendency to receive high thermal dose which means high ability to be killed by thermal dose. A decrease in perfusion at temperatures over 45 ° C resulting from heat-induced damage to blood capillaries can be observed then the value of perfusion rate at any location and time can be obtained using Arrhenius damage integral [Brown,1992]

$$\Psi(r,z,t) = \int_{t=0}^{t=t} A_{freq}\, e^{\frac{-E_a}{RT(t)}} dt \qquad \textbf{(11)}$$

where A_{freq} and E_a are presented for blood flow collapse(i.e. $_{freq}$ =1.98.10^{-6}sec^{-1}, E_a =6.67.10^{5}J mol^{-1} [24] ,then perfusion rate was then calculated continuously during the treatment as [24]

$$W(r,z,t)=W_o\,(1-e^{-\Psi}) \qquad \textbf{(12)}$$

2.6 Cases

To see the effect of focused diameter, two case had been studied, see table 3
only the targeted region is enlarge to see the effects of increasing the effected zone
While other parameters remins constant.

3.RESULAT AND DISCUSSION

The initial temperature distribution through tissue can be obtained from programe where no heat source is applied ,the resulting temperature distribution is as shown in fig 4, this can be obtained assuming an initial temperature throughout the tissue of 37°C, this steady state condition can be reached after 310 s from imposing convection heat transfer at the skin surface and only metabolic heat generation with perfusion coefficient are applied inside the tissue. This may verify the accuracy of this numerical simulation where the temperature of the skin surface is usually have a value of 33.5°C.

In spite the solution depends on certain factors, it can be generalized to study the effect of different parameters such as deep of cancer cell, induced power, attenuation coefficient and focused diameter. The intended zone and mesh used to determine temperature distribution is shown in fig 5, the fine mesh is required where severe gradient temperature distribution is expected. The acoustic window of ultrasonic source is located at the position where z=0.3 m so that the depth of 0.3 m is identical to z=0 m see fig 6. In human body the depth may not reach or exceed a depth of 30 cm but it is used here so that it may not affect the temperature distribution of ultrasonic path which we will see later

The temperature distributions when the maximum temperature is approximately don't exceed 60 ° and focused ultrasonic wave diameter of 2 cm are shown in fig 7 .Cutting off time is found to be 6 sec .The calculations are continue till the temperature in the entire zone is less

than $42^{\circ}C$ where below this temperature the volumes of nacreous cells can be neglected. This condition where the temperature in the entire zone is less than $42^{\circ}C$ can be reached within 310 s . Figure 8 indicates temperature distribution after 310 s where after that the temperatures in the entire zone are less than $42^{\circ}C$.

Different affected volumes had been seen to depend on the focal diameter. Assuming the same absorbed power density at the focal depth of 15W cm^{-3} but the focal diameter is larger than that for case 1 (which is known as case 2) then this will lead to affect a zone larger than that of case 1 as shown in fig 8.

A larger zone may be affected due to larger focal diameter. Fig 9, indicates the temperatures distribution for case 2 where the temperature is less than $42^{\circ}C$,this mission needs a time of 517.5 sec to be a achieved . It is clear that the time for the tissue to reaches $42^{\circ}C$ (after it was exposed to ultrasonic wave) is greater than that for case 1 since large amount of heat is induced to the human body in case 2.

Figure 10, indicates necrosis zone at 310 s for case 1 and 517.5 s for case 2. The necrosis volume had increased since temperature remains greater than $42^{\circ}C$ for a time longer than that it takes for case 1, assuming the zone of high temperature is larger than that for case 1. This will restrict the users of the ultrasonic wave tools to take care on the zone that must be affected precisely.

4. CONCLUSION

Even the theory of the cell necrosis and hyperthermia are well understood, the stand alone use of ultrasonic wave as a source of imposing heat into human body to kill cancer cell is rarely used. The controlling of the heat dose is the main factor in determining the affected zone by choose a suitable acoustic window, power and time.The required a suitable heat can be generating with a human body so as to kill the cancer cells where they may exist. A computer - aided device can be used to select precisely the region that must be targeted. Changing the focuse diameter may increase the effected volume where the cancer cell may exist. A suitable combination of ultrasonic wave source and computer program may be the most effective tools to kill the cancer cells and precisely strike the region by ultrasonic wave.

Table 1. Thermal properties of tissue and enviermental conditions

Convection heat transfer coefficient	10 W/ m^2.k
Environmen temperature	26 $^{\circ}$C
Density of blood	1060 kg/ m^3
Specific heat	3770 J/kg.k
Metabolic rate of tissue for skin	1 W/kg
Metabolic rate of tissue for fat	0.32 W/kg
Metabolic rate of tissue for muscle	0.67 W/kg

Table 2. Thermal properties of different kinds of human tissue[Torvida,1994]

Tissue	ρ (kg. m^{-3})	C (J kg^{-1} .$^{\circ}$K^{-1})	K (w m^{-1} .$^{\circ}$K^{-1})	W$_o$ (kg s^{-1} .m^{-3})
Epidermis	1200	3590	0.23	0.0
Dermis	1200	3300	0.45	1.35
Subcutaneous Tissue	1000	2675	0.19	1.35
Fat	900	3500	0.21	0.54
Muscle	1000	3500	0.642	2.3
Tumor	1000	3500	0.642	0.833

Table 3. Parameters for case-1 and case-2

Case number	d_f (m)	Z_t (m)	d_t (m)	μ (Np m^{-1})
1	0.15	0.1	0.02	5
2	0.15	0.1	0.03	5

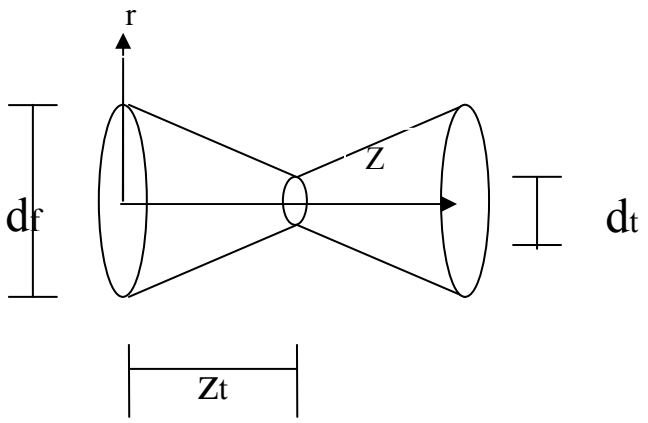

Fig 1. Schematic diagram of the acoustic widows

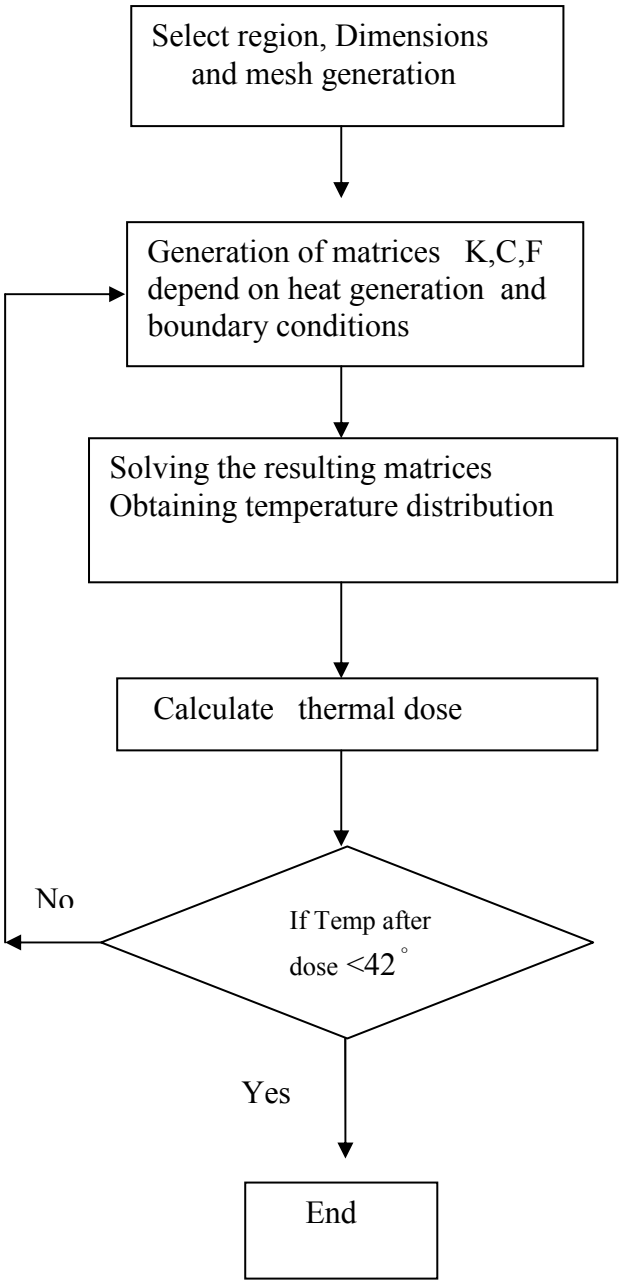

Fig 2. Block diagram for the program

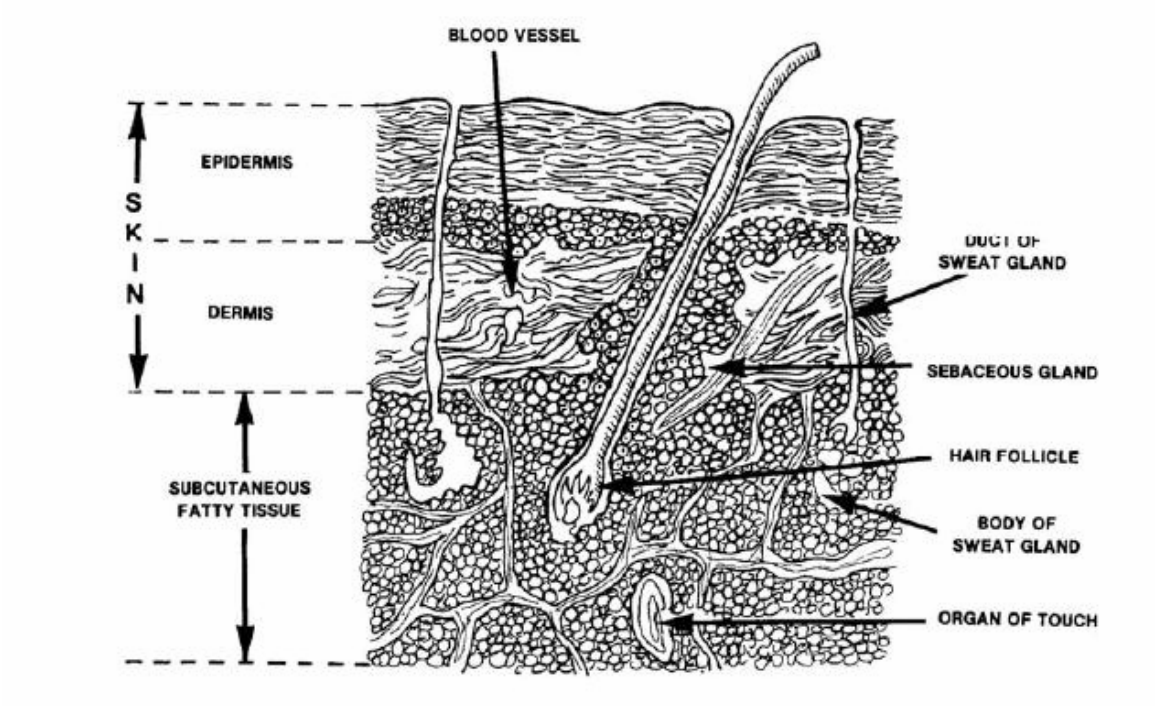

Fig 3. General structure of skin

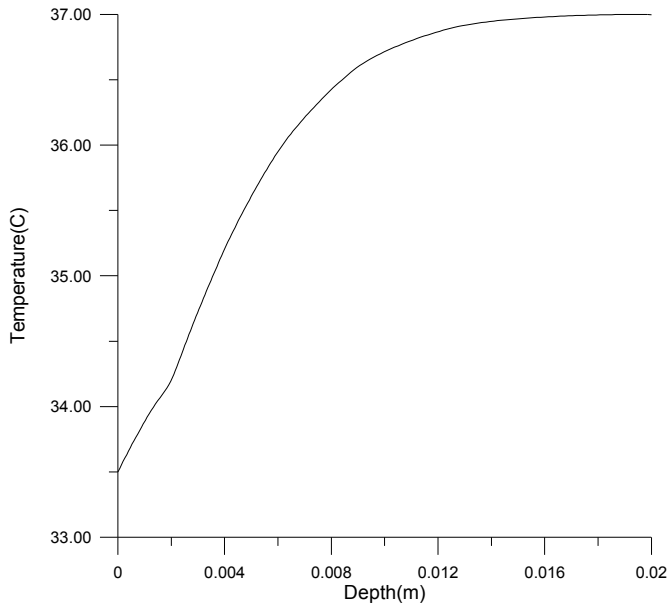

Fig 4. Initial temperature distribution across human body starting from epidermis

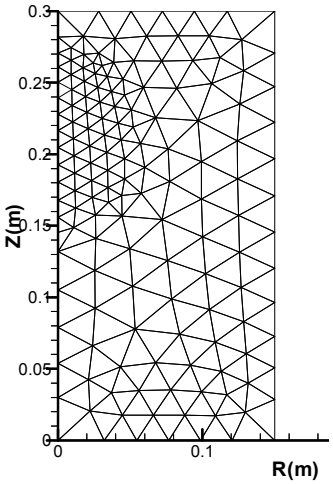

Fig 5 . Axis- symmetry mesh of the studied volume and boundary conditions

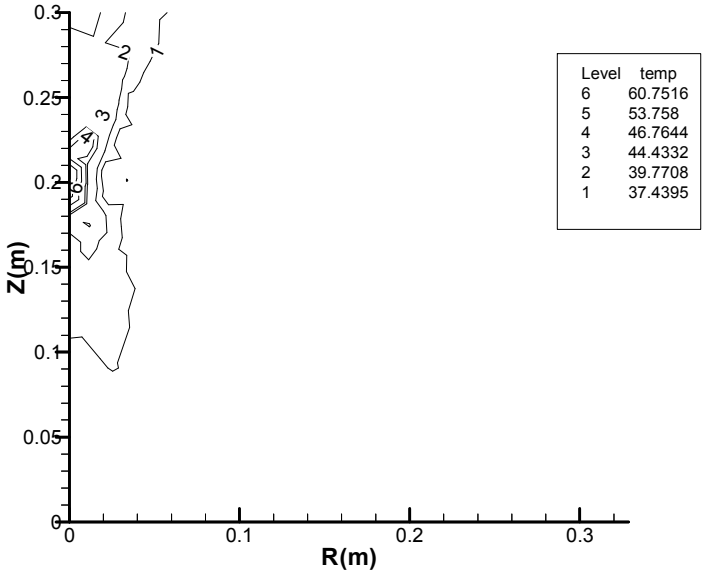

Fig 6. Temperature distribution through the studied axis-symmetry volume for focused diameter of (2 cm) after (6 s) Case-1.

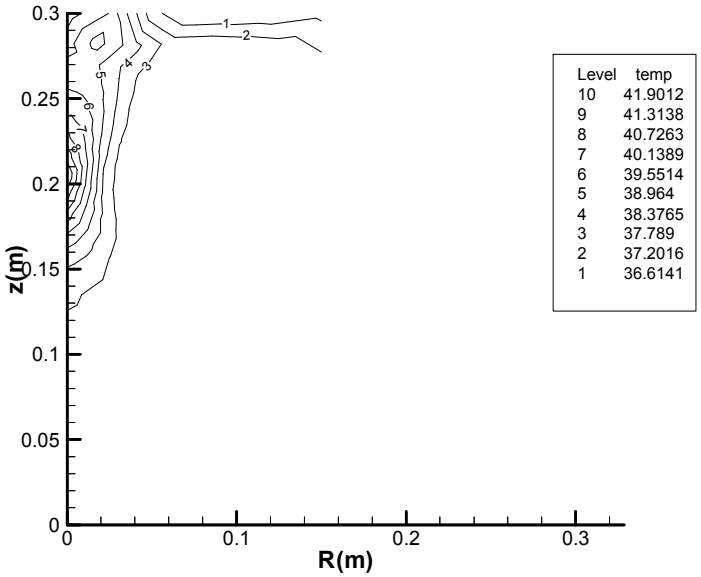

Fig 7. Temperature distribution after (310 s)for focused diameter of (2 cm) case-1

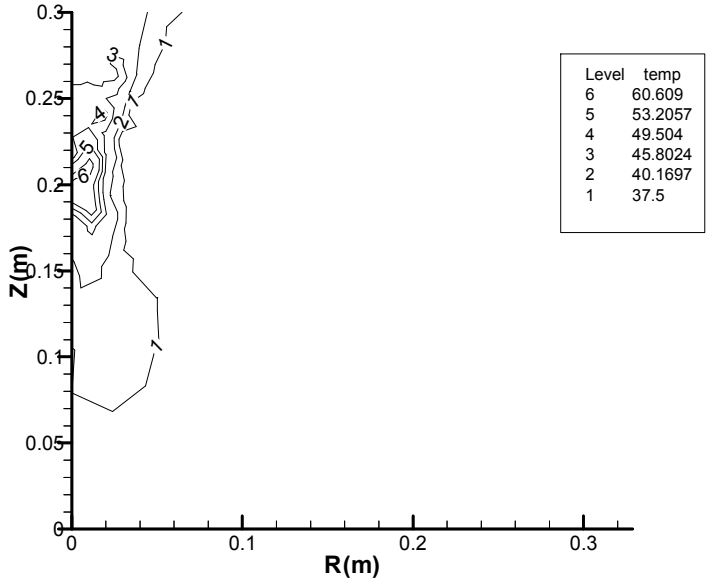

Fig 8.Temperature distribution for focused diameter of (3 cm)after(6 sec) case-2.

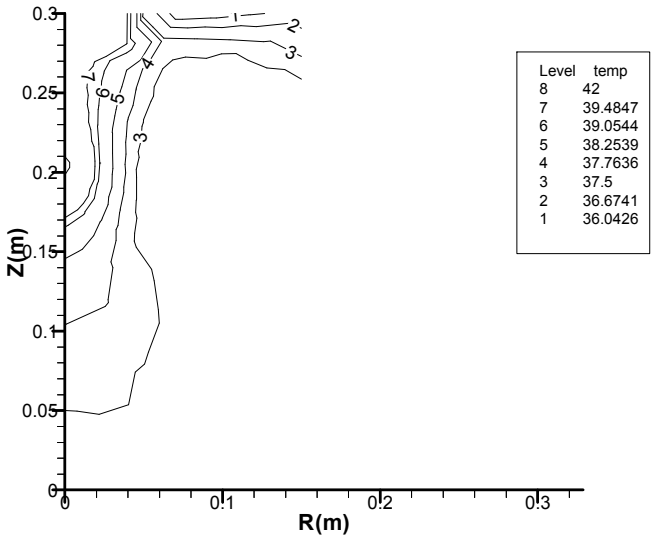

Fig 9. Temperature distribution for focused diameter of (3 cm) after (517.5 s) case-2.

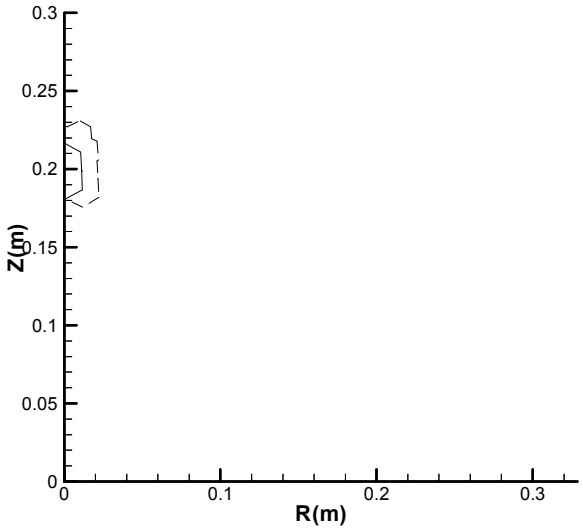

Fig 10.Necroses zone for case-1(solid line) and case-2 (dashed line).

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NOMENCLATURE

A-area(m^2)
A_{freq} -frequency factor(s^{-1})
c- specific heat ($J\ kg^{-1}.K^{-1}$)
d-diameter (m)
E_a -activation energy($J\ mol^{-1}$)
h-convective heat transfer coefficient($W\ m^{-2}.K^{-1}$)
I - power intensity ($W\ m^{-2}$)
k - thermal conductivity ($W\ m^{-1}.K^{-1}$)
N -shape function
q - heat transfer rate ($W\ m^{-2}$)
$\dot{Q}$ -heat generation per unit volume($W\ m^{-3}$)
Q_m -metabolic heat generation per unit volume($W\ m^{-3}$)
r -radial axis symmetry dimension (m)
S-constant in eq(10)
SAR- specific absorption rate($W\ m^{-3}$)
T - temperature ($^\circ C$)
t - Time(s)
TD - thermal dose (minutes)=eq(10)/60
W - perfusion rate ($kg\ s^{-1}.m^{-3}$)
z-longitudinal axis symmetry dimension (m)
[C],[K],[F] –matrices

Greeks

ρ - density($kg\ m^{-3}$)
μ - attenuation coefficient($Np\ m^{-1}$)
Ω -volume of interest(m^{-3})
Ψ - Arrhenius damage integral
Γ -surface of interest(m^2)
Δ - increment
∞ -environmental

Subscripts or Superscripts

b-blood
B-basal
f-final
m –metabolic
o-initial
p-total number of nodes
r- radial axis symmetry dimension
t- target region at focal depth
z- longitudinal axis symmetry dimension
n-1,n,n+1 time steps