A NEW APROACH FOR CONTROLLING THERMAL DOSE IN HYPERTHERMIA TREATMENT

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Abstract:
An optimal model based controller of the thermal dose in hyperthermia has been developed, using Pennes bio heat transfer function (which is a diffusion equation) as a plant model. Here in, a new approach is used to optimize the thermal dose of a simple scanned focused ultrasound transducer that satisfies the following aims: a)rising temperature of tumor region to 43 °c and keep it uniform during treatment . (It takes 30 to 60 minutes) . b) keeping the temperature of normal region near its initial value . c) using the minimum amount of energy. d) obtaining the optimal open loop controller that dose not need the invasive temperature measurements. This work demonstrates that the temperature can be made much more uniform by deposing greater amount of energy at the boundary of tumor than within the interior tumor region (it demonstrates in simulation part).

keywords: Control, diffusion equation, hyperthermia, optimization, scanned focused Ultrasound.

1. Introduction

Hyperthermia, the heating of tumor region, can improves the tumor treatment when it adds to radiation therapy or to chemotherapy [1] . Some clinical researches have been shown that the application of hyperthermia with radiotherapy improve the tumor response from 30% to 70% over radiotherapy alone[2].

The aim of hyperthemia is to elevate the temperature of tumor tissue volume to the target temperature (42°c to 45°c), while minimizing the temperature rises in normal tissue [3].

Controlling the thermal dose in hyperthermia is very important because when the pressure of amplitude of ultrasound propagation in tissue is increased over a frequency dependent threshold then gas bubbles form and collapsing the bubbles make shock waves and high temperature that destroys the normal cells [3].Several modalities have been used to generate hyperthermia such as radio frequency currents micro waves and ultrasound. Between these methods ultrasound is generally used because it has a much shorter wave length that makes the power penetration in deep tissue much easier and in addition several applicators have been developed for controlling its thermal dose [6] .

In 1970's ultrasound heating was tested clinically but importance of its control, focused scientists to work on different controlling methods and designing several kind of transducers . In recent years various control schemes have been used for controlling the temperature. Different kind of fuzzy systems such as takagi – sugeno fuzzy controllers, fuzzy self tuning

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controllers and fuzzy feedback controllers have been used [7-9] .The benefit of these fuzzy systems is that they do not require an explicit mathematical model of system on the other hand they have some disadvantages, as the number of membership functions are limited these systems can not obtain to precise answer and in most of these systems they are distributed by chattering problem. In addition some model based controllers like robust controller optimal controller, feedback controller, adaptive controller, bang bang controller have been used for hyperthermia [1,2,10-15], but they have some other inaccuracies too. Most of them are using finite element method that imposes the error of linearization to the system and another disadvantage is the force of using invasive temperature measurements to form a close loop controller that creates some pain and difficulties for patient.

In this work a new method has been introduced that has found the best amount of power satisfying the following means attending to boundary conditions and initial conditions that are mentioned before treatment. 1)solving the problem with arbitrary conditions. 2) proving the clinical rule of focusing power on boundary region to obtain uniform temperature.3) using a simple focused transducer, that is more available and more simple programming than other kind of applicators such as trapped linear phased array, sector vortex phase array and etc [6] 4) creating a meta center between different controlling aims. In section 2 mathematical model of heat penetration in body has been described section3 introduced the controller structure and section 4 simulates the results.

2.system description and mathematical model

The tissue temperature response is modeled using the Pennes' bio heat transfer equation (He did his experiments by putting some y shape invasive thermocouples as temperature sensors in human body and find the heat transfer equation so his model is so experlized)[16].

$$\rho c\frac{\partial T}{\partial t}=\nabla(k\nabla T)-w_b c_b(T-T_b)+Q \qquad (1)$$

c: specific heat of tissue (j / kg°c)
cb: specific heat of blood (j / kg°c)
wb: blood perfusion rate (kg/ m³ sec)
Tb: arterial temperature (assumed to be 37°c)
Q: power deposition in tissue
K: value of thermal conductivity
ρ : density

the numerical amount of these variables are given in table 1 [1,10]. In this work one dimensional model of tumor is considered obviously this model has some estimation errors because it decreases the measurement states specially when a non homogeneous tumor has been modeled, but this one dimensional model makes the mathematical practices much easier and increases the compatibility of method.

As you can see in figure 1 tumor has been modeled along the depth axes of patient's

Table1: numerical amount of variables in pennes transfer function

tissue	k	c=cb	W
Fat	.21	3500	.54
Tumor	.6	4000	.83
Bladder	.6	3500	5
Kidney	.577	3500	66
Liver	.64	3500	16
Muscle	.642	3500	2.3
Bone	.436	1000	.54
Aorta	.506	3500	83
Intestine	.550	3500	33

body that we name it X axes. We can rewrite (1) as one dimensional for [1,12]:

$$\rho c\frac{\partial T}{\partial t}=K\frac{\partial^2 T}{\partial x^2}-w_b c_b(T-T_b)+Q \qquad (2)$$

where x is depth axes and the position of applicator is usually mentioned by x=0 a region x ϵ [x0,xf] has been chosen such that it can include tumor region and some normal region surrounded tumor tissue.

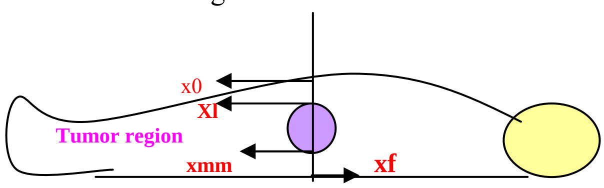

Figure 1.shema of a tumor in human body along x

3.1 Finding the optimal power deposition

To find the optimal power deposition that satisfies following aims, cost function J is formed as you can see in equation (3) a)satisfies equation (2)for given boundary and initial conditions. b) generates uniform temperature between42°c and 44°c without rising the temperature of normal tissue. c) be as minimum as it can.

so cost function J should be as follows:

$$J=a_1\int_0^{xf}\int_0^{tf}\|\rho(x)C(x)\frac{\partial T(x,t)}{\partial t}-k(t)\frac{\partial^2 T(x,t)}{\partial x^2}+w_b c_b(T-T_b)$$
$$-Q(x,t)\|dxdt$$
$$+a_2\int_0^{xf}\int_0^{tf}\|Q(x,t)\|dxdt$$
$$+a_3\int_{xl}^{xmm}\int_{t_0}^{tf}\|T(x,t)-43^\circ\|dxdt \qquad (3)$$

subject to

$$T(x,0)=37^\circ \qquad \forall x\in[0,xf) \qquad (4)$$
$$Q(x,0)=Q(x,tf)=0 \qquad \forall x\in[0,xf) \qquad (5)$$
$$\frac{\partial T}{\partial x}(0,t)=0 \qquad \forall t\in[0,tf] \qquad (6)$$
$$\frac{\partial T}{\partial x}(xf,t)=0 \qquad \forall t\in[0,tf] \qquad (7)$$
$$42\le T(x,t)\le 44 \qquad \begin{cases}\forall t\in[t_0,tf]\\ \forall x\in[xl,xmm]\end{cases} \qquad (8)$$
$$36\le T(x,t)\le 38 \qquad \begin{cases}\forall t\in[0,tf]\\ \forall x\in\{[0,xl)\cup(xmm,xn]\}\end{cases} \qquad (9)$$

where t0 is an initial time that is determined by operator and shows rise time of temperature for interior tumor region.

As you can see in figure 2 we choose x0, xf, xl, xmm such that xl and xmm define low boundary and high boundary of tumor(where x is depth axes) and x0, xn(=xf) are defining boundaries of normal region (x0 & xf are chosen by operator according to importance of normal region that surrounds tumor).We choose this parameters such that both two normal region in figure 2 be more than or at least equal to tumor region.

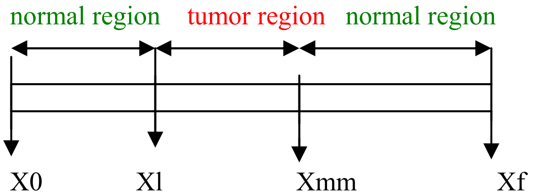

Figure2:.choosing value of xf, xl, xmm,x0 .

Equation 4 indicates that the initial temperature of body before treatment is 37°c equation 5 shows that the power deposition is zero at the first and at the end of treatment process . 6, 7 determine the flow of temperature in boundary of normal region and nonequivalent constrains 8 and 9 force the optimization to find the best power depositions that generates the temperature between 42 and 44°c in tumor region while keeping temperature of normal region in its initial value(one degree of tolerance in minimum time has been permitted) . A new approached method has been used to minimize the nonlinear cost function 3 using MATLAB programming. xf and tf have been divided to n and m partitions such that equation 3 rewrites as follows:

Minimize
$$j=\sum_{i=0}^{n-2}\sum_{j=0}^{m-1}\|\rho(i)c(i)(T_{i,j+1}-T_{i,j})\frac{m}{tf}-$$
$$k(i)\frac{n^2}{xf^2}(T_{i+2},j-2T_{i+1,j}+T_{i,j})+w_b c_b(T_{ij}-T_b)-Q_{i,j}\|\frac{xftf}{nm}$$
$$+\sum_{i=0}^{n}\sum_{j=0}^{m}\|Qij\|\frac{xftf}{nm}+\sum_{i=l}^{mm}\sum_{j=t0/m}^{m}\|Tij-43\|\frac{xftf}{nm}$$
(10)

Where [xl,xmm] is tumor region ;

[0,xl) $\cup$ (xmm,xf] is normal region

$$xl=l.\frac{xf}{n}\ ; \qquad xmm=mm.\frac{xf}{n}$$

lemma 1:

To solve a nonlinear optimization problem (like cost function *1 that has norm sign) with linear optimization methods we can rewrite norm of function f(x,t) in *1 with addition of two positive variable a and b, where f(x,t) is determined as a-b so we can optimize values of a and b with linear programming instead of using nonlinear programming to optimize value of f(x,t) .So $*_1$1 rewrites as *2:

$$\min\sum_x\sum_t\|f(xi,tj)\| \qquad (*1)$$
$$\min\sum_i\sum_j(aij+bij) \qquad (*2)$$

where aij,bij$\ge$0 and (aij-bij)=f(xi,tj)

According to lemma 1 we rewrite (10) by (11) to solve it by linear programming methods like LINPROG(in matlab) that are used more easily than nonlinear methods and take less time. In equation (11) Zij,Vij,Uij,Fij,Kij,gij are positive and *Z+V,U+F,K+g* are used instead of every norm sign in equation 10 where *Z-*

$V,U\text{-}F,K\text{-}g$ are defined in equations 16 to 18 and conditions (3) to (9)rewrites as (12) to (15) , (20) and (21) .

$$\text{Min } j=\frac{xftf}{nm}[\sum_{i=0}^{n-2}\sum_{j=0}^{m-1}Zij+Vij+\sum_{i=0}^{n}\sum_{j=0}^{m}Uij+Fij+\sum_{i=l}^{mm}\sum_{j=m/8}^{m}Kij+gij] \quad (11)$$

subject to

T(i,0)=37°c $0\le i\le n$ (12)

Q(i,0)=Q(i,m)=0 $0\le i\le n$ (13)

T(n,j)-T(n-1,j)=0 $0\le j\le n$ (14)

T(0,j)-T(1,j)=0 $0\le j<m$ (15)

$$Zij-Vij-\rho(i)C(i)\,{}^{m}\!/_{tf}\,(T_{i,j+1}-T_{i,j})+K_i\frac{n^2}{xf^2}\times (T_{i+2,j}-2T_{i+1,j}+T_{ij})-wbcb(T_{ij}-T_b)+Q_{ij}=0 \quad (16)$$

$$U_{ij}-F_{ij}-Q_{ij}=0 \quad (17)$$

$$K_{ij}-g_{ij}-T_{ij}+43=0 \quad (18)$$

$$Z_{ij},V_{ij},F_{ij},U_{ij},K_{ij},g_{ij},t_0\ge 0 \quad (19)$$

$$42\le T_{ij}\le 44 \quad \forall i\in[l,mm];\forall j\in[t_0,m] \quad (20)$$

$$36\le T_{ij}\le 38 \quad \forall i\in[0,l)\cup(mm,n];\forall j\in[0,m] \quad (21)$$

theorem 1 below proves that answer of equation (11) converges to that of main problem (3) as m and n tends to infinity as well as norm of x and t axes partitions(xf/n,tf/m) tends to zero.

Theorem1:

This theorem is an extension for one dimensional Riemann sum theory that proves completely in[17] . Partitions of two closed intervals (x∈ [x0,xf]:depth ,t∈ $[0,tf]$:time) are defined as two sets of P1 and P2 as follows:

P1={x0,…,xn}; P2={0,…,tm};

P(p1,p2)is the mesh of partitions and we write :

$\|P\|$=max {max(xi-xi-1:$0\le i\le n$,),

max($t_j-t_{j-1}:0\le j\le m$)}

then we choose a xxi in each interval [xi,xi-1] and a ttj in each interval [tj,tj-1] and height of f(xxi,ttj) is used to approximate the surface under the f(x,t) over the interval [xi,xi-1]and [tj,tj-1].The erea of this cubes are approximated by Riemann sum as follows:

$$S=\sum_{i=0}^{n}\sum_{j=0}^{m}f(xxi,ttj)\,(\text{xi-xi-1})(\text{ tj- tj-1}) \quad (22)$$

If the intervals is subdivided more finely the subintervals in the partition have shorter lengths then the Reimann sum should give the better approximation and as $\|p\|$ converges to zero S converges to a double integrated equation(it's prove is obvious according to Reimann theorem). In[17] we have a definition:

The function f is Reimann integrable over x∈ [x0,xf] and t∈ $[0,tf]$ if there is a number of A∈ R with the property that for eachϵ>0,there is δ>0 such that P is any partition of [x0,xf] and $[0,tf]$ with mesh $\|P\|$< δand so we have

$$|\,S(f,P,\{xxi,ttj\})-A\,|<\epsilon \quad (23)$$

So the following equation is proved:

$$\lim_{n,m\longrightarrow\infty}\sum_{i=0}^{n}\sum_{j=0}^{m}f(xxi,ttj)*(\text{xi-xi-1})*(\text{ tj- tj-1}) =\int_{x=x0}^{xf}\int_{t=0}^{tf}f(x',t')\,dt\,dx' \quad (24)$$

3.2 finding the optimal controller

It is important to mention that the only controllable variables that can shape the optimal Q are power intensity and position of transducer . These parameters have the following relationship[18] :

$$Q=2\alpha I(0) \quad (25)$$

where α is absorption factor, I(0) is intensity on body surface and Q is power deposition . α demonstrates as[1,12] :

$$\alpha=\alpha_i[\frac{r}{r-x}\sin(\frac{\pi d^2(r-x)}{8\lambda xr})]^2e^{-\alpha_i s_i} \quad (26)$$

$$Q=2I(0)\alpha_i[\frac{r}{r-x}\sin(\frac{\pi d^2(r-x)}{8\lambda xr})]^2e^{-\alpha_i s_i} \quad (27)$$

where r is radius of curvature, and λ is wave length and d is the diameter of the transducer. for our special transducer λ=.001m and r=.25m, d=.7m and $\alpha i=20.5$ for tumor region and 18.5 for normal muscle tissue.

Figure 3 and 4 show the schema of a simple focused transducer and its power deposition in body for a transducer 17cm from body surface with I(0)=8000(w/m^3) according to (23)[1,12,18].

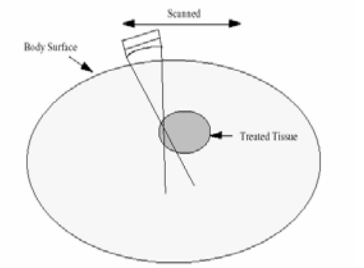

figure3: a simple focused transducer

to find the best controller , Q is obtained for every partitions of t as you can see in figure5. And as it has shown in clinical results (and in figure 7) Q(x) has only two maximum for all amounts of t that are positioned on tumor boundaries (xl,xmm) so to find the best controller we obtain the mean ofQ(x) for all m-1 partitions of t ($t \in (0,tf)$) that is always a diagram with two peaks on tumor boundaries. One example is shown in figure 5 which is the mean diagram of Q that has been shown in figure 7 of simulation part..It is obvious that

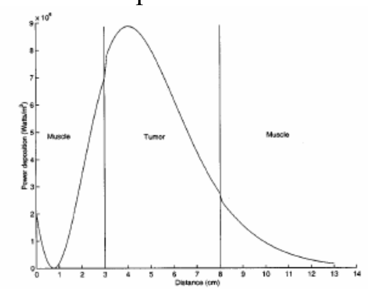

figure4: power deposition for I(0)=8000(watts/m^3)

we can produce the best power deposition for every one dimensional tumor by using only two coupled simple focused transducer that are positioned on x_I and x_2 cm from body surface with power intensity of I_1 and I_2 that can be found as follows:

To find above parameters we estimate figure 5 with two bell shape diagrams that can satisfy equation 27 as you can see in figure 6. We use two main constrain to determine bell shape diagrams Q1 and Q 2 , so we can find a good estimation by considering 2 simple constrain as follows: 1)the bell shape diagrams and real averaged diagram should have the same peaks as you can see in figure 6. 2)if we name the contact point of Q1 and Q 2 by xc and we name the average diagram of figure 5 by Qav we should choose Q1 and Q2 such that :

Q1(xc)=Q2(xc)=.5*Qav(xc)

So Q1 and Q2 are fined easily from equation 27 by considering above constrains.

to find peaks of Q1 and Q2 we have:

$$\frac{\partial Q_1}{\partial x} = 0 \qquad \frac{\partial Q_2}{\partial x} = 0 \qquad (28)$$

where Q1 and Q 2 are two bell shape diagrams. Equation (28) has one root for each Qi that demonstrate two peaks of power deposition. If we name these roots by x_{z1} and x_{z2} then x_I and x_2 can be found:

$$x_I = x_{z2} - xmm \qquad (29)$$

$$x_2 = x_{z1} - xl \qquad (30)$$

according to figure 6 I_I and I_2 are determined:

Q1(I(0)=I1, xl) =hh so I1 is found (31)

Q2(I(0)=I2, xmm) =hf so I2 is found (32)

Above method is used for a patient in section 4.

4.simulation

This method has been simulated on a tumor in depth of 10cm from body surface with radius of 2.5 cm so normal region is determined as [0,20]cm (depth from body surface)and tumor region is [14,15]cm (we use m=20 and n=20 for this problem) figure 7 and 8 shows the best power deposition and temperature of body along depth axes. Obviously results satisfy the goal of treatment very well with a simple shape power deposition.

Using (29) to (32) x1,x2, I_I and I_2 obtained as follows:

xmm=15cm ; xl=10cm; x1=10cm; x2=6cm;

hh=2.3*10^5;hf=2.3*10^5;I_I =950; I_2 =2750;

Where d=.9cm and r=20cm . figure9 shows Q1 and Q2 that are obtained from mentioned parameters. As you can see (in figure 9) optimal power intensities cause some sinusoidal signals in normal region ($x \in [0,.1) \cup (.15,.2]$cm) that makes real Q1 and Q2of figure9 different from the optimal Q1 and Q2 that are shown in figure 6 but this difference is negligible because sinusoidal signals in normal region have small amplitudes in compare with two main peaks of Q1 and Q2 so this error will increase temperature of normal region very weakly. Figures 7 to 9 shows that results satisfy the goal of treatment very well .(one advantage of this method is that bothQ1 and Q2 can be constructed by one transducer and we should just control intensity and distance of transducer from body)

5.conclusions

Some problems such as damaging normal tissue, long treatment time with low efficiency, and changing temperature of tumor tissue during treatment shows that optimization of controllable parameters during treatment is so important. Compare with previous hyperthermia controllers this new approach method has the following advantages: 1) find the best controller by considering the initial conditions of normal and tumor tissue which leads to find the best controller for each person withdifferent biological conditions. 2) keep the normal tissue on its initial value while causing a uniform amount of temperature in tumor with a great efficiency. 3) cause a multi objective controller which rises thetemperature by using minimum amount

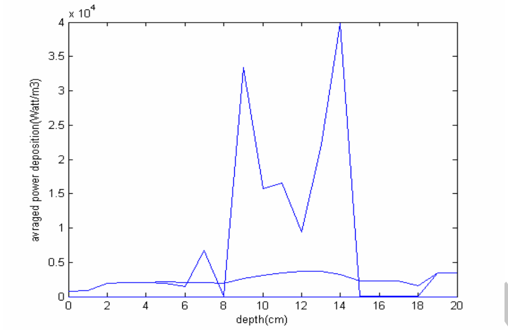

figure5:average of power depositions for each time partitions

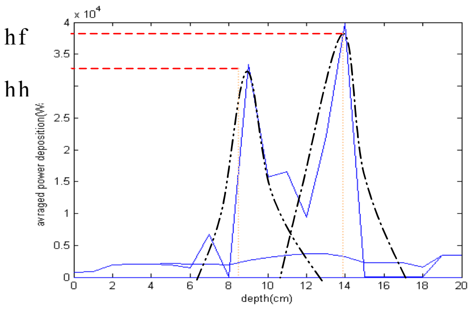

figure6: estimation of figure 5

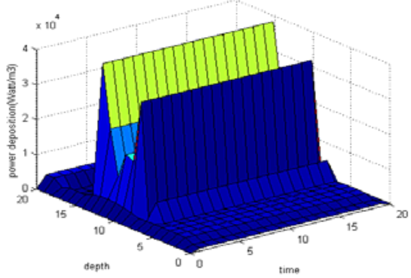

figure 7 :power deposition for a tumor region

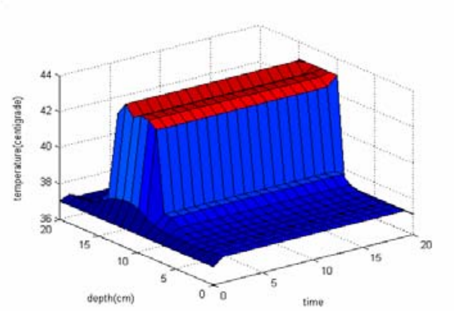

figure 8:temrature penetration in human body

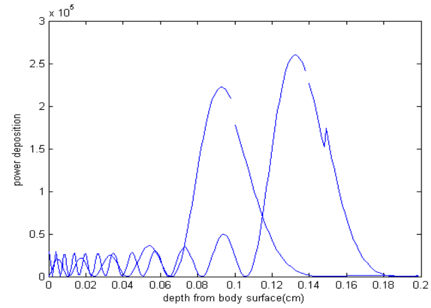

figure 9 :power deposition Q1 and Q2

energy while satisfying main aims oftreatment and possibility of changing importance of objective by changing their weight in cost function. 4)use a new method to find the best parameters that is simple and easy to solve by MATLAB or LINGO programming. 5) have less error than linearization methods such as finite element.

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REFRENCES

1." Model predictive control of ultrasound hyperthermia treatments of cancer"; Dhiraj Arora, Mikhail Skilar, Reomer; IEEE 2002

2." A control strategy for hyperthermia ";J.Kyle,Hal Tharp;IEEE 1993

3." Review of ultrasound therapy "; Kullervo Hynynen ;IEEE 1997

4." Principles of hyperthermia "Principles of radiation oncology, section11, Daniel S.Kapp , Mdgerge M. Hahn, Robert W.Carlson

5. " Principles and practices of radiation and oncology"; Carlos.A.Perez, Luther Wbardy,

6. " New 2D ultrasound phased array design for hyperthermia cancer therapy";Hasan Sharifi,Hamid Soltanianzadeh;2003

7." Theoretical analysis of a takagi-sugeno PI controller with application to tissue hyperthermia therapy", Yongsheng Ding, Hao Ying, IEEE, 1998

8." A fuzzy system for Real-time control of tissue temperature during laser heating" Yongsheng Ding, Hao Ying,IEEE,1998

9." Fuzzy self tuning immune feedback

controller for tissue hyperthermia" ;Lihong Ren, Yongsheng Ding; IEEE 2000
10." Impact of nonlinear heat transfer on temperature control in regional hyperthermia"; Jens Lang, Bodo Erdmann,IEEE 1999
11." Exact temperature tracking for hyperthermia : A model-based approach"; Marshall Mattingly, Robert Roemer,Santosh Dev asia ;IEEE 2000
12." Model predictive control of hyperthermia reatments", Dhiraj Arora, Mikhail Skilar, Reomer; IEEE 2002
13." Feed back control of temperature during hyperthermia treatments with phased array ultrasound applicators"; P.VanBaren, E.Be C. A. Cian; IEEE 1997
14." Control of phased arrays for hyperthermia using thomographic temperature feed back ; m.e.kovalski, J.M.Jin,IEEE 2001
15." Apoplication of extended kalman filtering to hyperthermia"; J Kyle Potocki, Hal S Tharp; IEEE 1992
16." Analysis of tissue and arterial blood temperature in the resting human forarm"Journal of applied physiology,1948
17." Introduction to real analysis "; D. Depree ,1993