Application of the ultrasound hyperthermia model for a multi-layered tissue system

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Abstract. This work models the thermal effect of several planar transducers targeting the tumour interactively in a ceramics-coupling-skin-muscle-tumour system. The most important inputs of the model include the following: emitted electric output, J/s; mechanical efficiency, %; number of transducers, pieces; surface area of the transducer, m²; area, m² and temperature, K of the cooling surface, attenuation coefficients, Np/cm MHz; specific heats, J/gK; densities, g/cm³; heat conductivities, J/msK; sound velocities m/s; flow rate of blood in the tissues, ml/g tissue/min; sound path in the tissues and in the blood flowing through the tissues, m. From the inputs, a number of intermediate data are determined, e.g. the geometry of the irradiated bodies that are in the path of ultrasound, acoustic hardness, Pas/m; sound reflection and sound transmission occurring at the interfaces, Np; heat exchanger wall thickness of the irradiated bodies, m; heat dissipation and heat exchanger surface areas, m²; flow rate of blood in the tissues located in the path of ultrasound, ml/tissue mass in g/min; and the sound attenuation of the tissues, Np. The amount of generated heat, K/s decreased by the heat energy transported, J/s to the surrounding tissues by blood and heat conductivity, and the actual temperature, K of the irradiated tissue are the output parameters calculated by the model. The output results are available in the form of functions. The expected temperature of the target area, K can be set to either the denaturation temperature or to the respiratory decomposition temperature (43.5°C) without damaging the surrounding tissues by setting in the following parameters properly: electric output power, W; the number and surface area, m² of the transducers; the area, m² and temperature, K of the cooling surfaces. After further development, the model will be suitable for handling more than three tissue layers, increased blood flow rates different angles of incidence, and tumours having different geometric shape.

1. Introduction

Due to the inadequate blood supply of the tumour, these are heated to higher temperature than the healthy tissues under the irradiation conditions. By increasing the temperature of the cells by irradiation, intensity of their aeration increases, but as their blood supply is inadequate, as a result of the irradiation, the cancerous cells die due to lack of oxygen [1]. The most suitable temperature range for treating cancerous prostate cells is 43-45°C and the length of the effective treatment shall be between 30 and 60 minutes [2]. High intensity focused ultrasound has two types of effect. One of them is the lesion or cut that spreads in a regular way in the focus by way of heat coagulation. The other effect is that vapors are generated in the focus and these vapors rapidly expand towards the ultrasound source [3]. Linear model was applied for studying the effect of heat generated in the tissues by ultrasound [4], but they could not reproduce the heat effect of the treatment accurately by means of this model. Non-linear models based on e.g. the KZK equations were applied by [5]. The table 1. showed the most usual applied US HT temperatures.

| Temperature (°C) | Description |
|------------------|-------------|
| 40               | Denaturation temperature |
| 43.5             | Respiratory decomposition temperature |

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Table 1. The thermal intervals of the different US hyperthermia systems.

| Type of the US       | Author  | Effective thermal interval |
|----------------------|---------|---------------------------|
| Scanned US [6]      |         | 40.0-44.4°C               |
| Scanned US [7]      |         | 39.9-43.1°C               |
| Multielement US [8] |         | 38.5-42.7°C               |
| Transrectal US [9]  |         | 40.5-43.2°C               |

1.1. Goals of preparing the hyperthermia model
The goal was to develop expandable interactive software for modeling respiratory and denaturizing hyperthermia that can predict the effect of heat generated by more than one ultrasound beams passing through the tissues. The model shall be capable of handling the adjustments of the independent variables during the modeling process, and the applied functions shall be compatible for the individual tissues. The model shall calculate the intensity changes of the sound beam, the occurring losses and, from the remaining intensities, the effect of heat.

2. Materials and Methods
2.1. Guidelines
The model examines the effect of heat generated by a transducer, which consists of a definite number of rectangular crystal elements, on a specific volume element, while the sound passes through a given number of tissue layers (skin, muscle, tumour) having specific features. The model takes into account the beam intensity modifying effect of the individual body tissue layers. It calculates the heat generated in the tissue volume elements after correcting it by the heat energy removed by perfusion of blood, by the cooled transducer and by the neighboring tissues. A feature of the model is that the heat energy draining effect of a 10 minutes long pre-cooling step on the examined tissues can also be included in the calculations, so it can be used in a more flexible way in examining the effects of different ultrasound intensities and of different number of transducers applied to avoid denaturizing of healthy tissues caused by excessive heat. Of course, cooling can be applied continuously during the whole treatment period. The type of the tissue layer is represented in the model by its acoustic and thermal parameters. Such decisive parameters are the propagation velocity of sound in the individual tissues, their specific heat, density, attenuation coefficient, heat conductivity and the perfusion rate of blood in the subject area. The amount of heat generated that depends on material properties is determined by the geometry of the irradiated tissue bodies and by the irradiation parameters (intensity, frequency, wave shape, mode, the extent of focusing) and by the occurred losses.

2.2. Tissue geometry
During the calculations that conventional assumption was applied that the incidence of the beam is perpendicular to the tissue layers, as shown in figure 1. The beam transmission surface is $S=ab$, cm$^2$, where the width and length of the transducer, are $a$ cm and $b$ cm, respectively, and the treated tissue volume $V=Sh$, cm$^3$ is the function of the $S$ surface and the tissue thickness $h$, cm. Based on $M=V\rho$, the mass of the treated tissue can be calculated expressed in g, where $\rho$, g/cm$^3$ the density of tissue. From the product of the treated tissue mass and the specific heat of the tissue, the energy needed for increasing the temperature of the subject tissue by 1K can be arrived at $C$, J/gK in a unit of measurement of J/K.

2.3. Perfusion rate of blood
The information on the volume of the treated tissue is also important due to the perfusion rate of blood, as in addition to the literature data ml/g tissue/min ($B_1$), the g blood/g actual tissue/min ($B_2$) value shall also be determined and this requires the knowledge of blood and tissue densities and the treated tissue volume. In a conventional way, when using the perfusion rate of blood/minute value, the model assumes that this is the quantity of blood that is present in the subject tissue at any time. Of course, the
realistic value may differ from this quantity and this blood quantity changes further during the treatment as a result of the increased perfusion rate and heart rate. Due to this, the perfusion rate of blood is considered by the model as an input parameter, that is it can be adjusted for the individual tissues. The length of the path of the sound beam in the blood flowing through the tissues is also a factor of decisive importance. This means that the height of blood in the irradiated tissue volume determined by the irradiation surface $S$, cm$^2$ and the thickness of the specific tissue shall be determined. This corresponds to those assumptions that the vascular system of the tissues is so dense and the walls of the blood vessels are so thin, that the heat exchange between the tissues and blood can be considered instantaneous. As a consequence of this, it is enough to determine the quantity of blood in the treated tissue volume having a specific surface, and through this to determine the height of the blood body in the tissue, $h_b$, cm with formulae $h_b=(B_S/p_{hb})/S$ in order to calculate the heat generated in the blood present in the tissue by the irradiated acoustic energy, and to correct the generated heat $J/s$ by heat energy factors representing the quantity of heat transported to, and from, the treated tissues by the perfusion of blood.

2.4. Intensity functions

In order to determine the different intensity changes, the sound intensity is calculated in the following units of measure: W/cm$^2$, dB and Np. From the emitted total electric intensity $I_e$, W=J/s, the initial acoustic intensity $I_i$ can be calculated by using the initial acoustic intensity, W and the electro-acoustic coefficient ($\eta$, %) of efficiency according to equation $I_e=I_i\eta$. The acoustic intensity per surface unit in W/cm$^2$ can be calculated from formulae $I=I_e/S$. Traditional way of recalculating this variable in dB unit of measure is shown by the equation $I_{dB}=10\log_{10}(I_e/I_0)$ where $I_0=10^{-16}$W/cm$^2$. Recalculation of $I_{np}$ from this equation is described by $I_{np}=I_{dB}/8.686$. Of course, the units of measure can also be recalculated backward using the inverse forms of the appropriate equations. Attenuation caused by the specific tissue volume can be calculated by $I=I_0e^{-2\alpha h}$ where $I_0$ is the actual Np intensity and $I_0$ is the initial intensity expressed in Np, $\alpha$ is the attenuation coefficient (Np/cmMHz), and $h$ is the length of the path of the sound beam in the given medium expressed in cm. From here the model calculates the W/cm$^2$ intensities for each media backwards through $I_{dB}$ then it determines the reflections $R$ at the medium interfaces and through this, the transmitted intensity $T$. If it is assumed that the incidence is perpendicular to the interface between the media, the rate of reflection is $R=(Z_2-Z_1)/(Z_1+Z_2)$, which is a function of the difference between the acoustic hardness (Pas/m) of the media $Z=c\rho$, where $c$, m/s is the sound velocity, $\rho$, g/cm$^3$ is the density, $Z_1$ and $Z_2$ are the acoustic hardness of the resultant and receiving media, respectively. From these results the level of relative sound intensity transmitted through the interface can be calculated from $T=1-R$, provided that $1=100\%$. that is in the absolute acoustic intensity, the acoustic intensity going through the interface between the media is $I_T=I_T$ in W/cm$^2$. The heat energy generated in the examined tissue [10] volume can be calculated by the equation $dT/dt=2\pi dI/C\rho$, K/s, provided that both the numerator and the denominator of the formula have been corrected by the distance covered and by the treated tissue volume, respectively. By solving this equation to sec K can be arrived at, namely the result show how much the temperature increases in the system in a given period of time where $C$ is the specific heat JgK of the examined tissue. The reason why the Rayleigh-Sonnerfeld [11] equation, the equation that handles $xyz$ coordinates was not used in the model is that our goal was to calculate the spatial average temperature of the tissue volume to be treated and the model assumes that the position of the tissue volume to be treated is known, because this is the location where the transducers are focused to. If the calculation was carried out on the basis of the $xyz$ coordinates, the application of the bioheat transfer equation (BHTE) of Pennes [12] and [13] would be necessary, although this equation does not deal with the presence of blood vessels and the changes in the perfusion rate of blood that occur during the treatment. The equation systems applied in the model are equivalent with the BHTE system without space coordinates and they take into consideration the input (feed energy) and output (losses) sides of the energy balance. The acoustic intensity reaching the tumour can be calculated as a sum of the residue intensities of all the transducers.
focused to the tumour, without considering the interferences. Generated heat is determined from this intensity by time units. Basic spatial scheme of the hyperthermia superstructure is shown in figure 1.

![Spatial scheme of the US HT superstructure.](image)

**Figure 1.** Spatial scheme of the US HT superstructure.

### 2.5. Losses

When determining the heat generated in the treated tissue volume during the ultrasound irradiation, two factors shall be known: these are the level of heat energy generated by the acoustic energy of the continuous input radiation and the level of heat loss. Three main sources of energy loss are handled by the applied model. These are parts of the energy removed by blood ($I_b$), by the cooled transducer surface ($I_t$) and by the heat transported to the neighboring tissues ($I_c$) by heat conduction. Determination of the latter two sources of loss ($I_t$ and $I_c$) are based on determining the heat flow $I$, J/s along a planar heat exchanger wall surface by using the equation $I=\lambda/w[S_q(t_1-t_2)]$ where $\lambda$, J/msK is the heat conductivity of the given tissue, $w$, m is the wall thickness of the heat exchanger, $S_q$, m$^2$ is the size of the heat transfer surface, and $t_1$, K is the actual tissue temperature or the average temperature of the internal tissue volume. $t_2$ is the external temperature prevailing on the wall of the heat exchanger that is usually considered as 310K, that is 37°C body temperature by the model when calculating the heat conducted towards the neighboring tissues. For a rectangle, calculation of the $w$ wall thickness of the heat exchanger is done by formulae $w=\left(\frac{a}{2}+\frac{b}{2}+\sqrt{a^2+b^2}\right)/3$. When determining the $q$, J/s heat flow towards the neighboring tissues, the $S_q$, m$^2$ heat exchange surface means the skirt surface of the irradiated tissue volume given by the formulae $S_q=\left(\frac{2ha}{10000}+\frac{2hb}{10000}\right)$, except in the case of the last tumour layer where the heat exchanger surface located opposite to the beam entry surface shall be added to the calculated surface. In the case of the $I_c$ heat energy removed by the cooled transducer the wall thickness and the heat exchanger surface are equal to the depth of the treated tissue expressed in m and to the surface of the transducer or the $S$ surface to the treated tissue volume, respectively. In case of the top layer, the cooling surface can be adjusted and a cooling surface different from the transducer surface can be applied if necessary. In case of the $I_c$ heat flow removed by the cooled transducer the $t_1$ temperatures of the individual layers are equal to the respective temperature of the contamination interface of the layer located above the subject layer in the point of time just preceding the point of time to which the calculation is made. The energy removed by blood $I_b$, J/s can be calculated from the difference of the introduced and removed energies according to the formulae $I_b=\left(\frac{t_1B^2C_b}{2}\right)-\left(310B^2C_b\right)$, where $C_b$, J/gK is the specific heat of blood and $t_1$ is the average internal temperature of the currently treated tissue mass.

### 2.6. Complex equation

Based on the above, the heat generated by the ultrasound in the individual tissue layers can be calculated from the (2.6.1.) equation:

$$
\frac{\partial T}{\partial t} = \frac{2\alpha_b h_b[J_S-(I_c+I_t)]}{C_b \rho_b V_b} + \frac{2\alpha_f h_f[J_S-I_b]}{C_f \rho_f V_f}
$$

(2.6.1.)

where indices $b$, $t$ and $c$ refer to blood, tissue and cooling surface, respectively, and the result given in K/s. In the equations $I_b$, W/cm$^2$ is the value of acoustic intensity at the tissue interface. This value shall
be multiplied with the irradiated surface ($S$, cm$^2$) to calculate the total intensity arriving into a volume element. $I$, J/s, $I_{cooling}$, J/s and $I_b$, J/s represent the heat flow towards the neighboring tissues, the heat flow towards the cooled transducer surface and the tissue interface located above the subject tissue layer, and the heat removed by blood, respectively. Treatments are carried out by the model by sine waves at a frequency of 1 MHz, but the frequency can be adjusted. This means modification of the attenuation coefficient $a$, Np/cmMHz.

2.7. Basic data
The most important independent variables used in the equation systems, based on their respective indices, are the following: $c$, ceramics; $co$, electro-acoustic coupling; $s$, skin; $m$, muscle; $t$, tumour; $b$, blood. Attenuation coefficients: $a_c=0.24$; $a_{co}=0.15$; $a_s=0.085$; $a_b=0.019$ in Np/cmMHz; the sound velocity values: $c_c=2220$; $c_{co}=6320$; $c_s=1720$; $c_m=1566$; $c_t=1549$; $c_b=1566$ in m/s; the specific heat values: $C_c=3.66$; $C_{co}=3.639$; $C_s=3.9$; $C_m=3.89$ in J/gK; the heat conductivity values: $\lambda_c=0.37$; $\lambda_{co}=0.55$; $\lambda_s=0.545$ in J/msK; the density values: $\rho_c=7.6$; $\rho_{co}=2.7$; $\rho_s=1.01$; $\rho_m=1.04$; $\rho_t=1.04$; $\rho_b=1.06$ in g/cm$^3$; $B_{1c}=0.2$; $B_{1m}=0.027$; $B_{1t}=0.25$ in ml/g tissue/min. Parameters affecting the heat effect of the treatment were the following: coupled out total electric intensity, W; width and length of the transducer, m; number of transducers focused to the tumour (pieces); cooling surface of a transducer, m$^2$; temperature of the cooling surface, K; thickness of skin, muscle and tumour layers, respectively, m; coefficient of acoustic efficiency of the transducer, %.

3. Results and discussion
In the most cases the goal is to achieve and keep an approximate temperature of 315 K in the blood-tumour system during the ultrasound hyperthermia treatment. If high unit intensity is applied without surface cooling, it can be seen that the skin-blood, or even the muscle-blood systems will be extremely overheated and this may cause denaturizing (figure 2). In order to avoid this negative effect, pre-cooling of different intensity can be applied in the tissue systems by applying cooling surfaces having different sizes or by applying more than one transducers having lower intensity that are focused on the tumour (figure 3). It can be seen that as a result of the application of higher number of transducers, cooling surface and of a cooler temperature of 283K positive result can be achieved in respect of the above goal. In addition, it can be seen that the tissue layers used in the model are thick. If the thicknesses of the tissue layers are considered ideal, smaller cooling surfaces, higher cooler temperature, lower number of transducers and lower intensities are appropriate for the hyperthermia treatment of required length (figure 3).
Figure 3. Evidence of the fact that of tumours located near the body surface can be treated effectively by ultrasound hyperthermia treatment.

4. References
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