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Theoretical and experimental evaluation of high temperature ultrasound in cancer therapy

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The University of Arizona, 1993
THEORETICAL AND EXPERIMENTAL EVALUATION OF HIGH TEMPERATURE ULTRASOUND IN CANCER THERAPY

by

Christakis Andrea Damianou

A Dissertation Submitted to the Faculty of the
DEPARTMENT OF ELECTRICAL AND COMPUTER ENGINEERING
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1993
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Christakis Andrea Damianou entitled Theoretical and Experimental Evaluation of High Temperature Ultrasound in Cancer Therapy and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director

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SIGNED: ___________________________
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ABSTRACT

The purpose of this study was to use the concept of calculated thermal dose to predict the necrosed tissue volume, and to evaluate the near-field heating due to application of multiple pulses to cover a large volume. In addition, overlaying tissue damage cause by sonicking a highly-perfused tissue seated only a few cms deep was evaluated. The thermal dose distribution during focussed ultrasound exposure was calculated based on numerical models used for calculating ultrasound power distributions and the resulting temperature distributions in tissue. In vivo experiments in dogs and rabbits were conducted to obtain the reliability of the predictions.

It was found that the lesion intensity threshold was almost independent of the frequency for transducers with an F-number of 1. It was found that the lesion size was practically perfusion independent for pulses 5 s or shorter. The lesion size increased with increasing pulse duration, acoustical power, and F-number, but decreased with increasing frequency at a constant focal intensity. The results shown in this dissertation can be used as a guide for selection of transducer parameters for ultrasonic surgery.

The temperature elevation in the near-field was evaluated. It was found that significant delays (20 s or longer) between the pulses must be introduced in order to avoid unwanted tissue damage in front of the focal zone. In addition, decreasing the pulse duration and F-number reduced the temperature elevation in front of the focus.
It was shown that the damage to surrounding tissues when sonicating a highly-perfused tissue (such as kidney) seated a few cms deep, can be avoided by using a transducer with an F-number of 0.8 and a frequency of about 1 MHz. The heating of the surrounding tissues can be reduced more by correct selection of the pulse duration and power.

The tissue necrosis due to ultrasound was monitored using MRI imaging. A study of MR signal intensity change with temperature of dog and rabbit tissues in vitro showed that MRI has the potential to monitor temperature non-invasively. The signal sensitivity with temperature was found to be about 1.2-1.7 %/°C.
INTRODUCTION

The use of heat in cancer treatment was applied years ago (3000 B.C.) [1], when cautery was used as a means of destroying tumor cells. Later this technique was abandoned, probably because of the severe pain involved following or during the procedure. The application of heat in cancer was continued, but the goal was to use lower temperatures (to minimize pain) somewhere in the range of 42-45 °C (a similar goal with current hyperthermia treatment modalities). The possibility that the low-temperature technique had therapeutic effect was first reported by Busch in 1886 [2]. His speculation was based on an observation of a patient with sarcoma of the face, that completely disappeared after a high fever. Other investigators reported similar regression of tumors due to fever. Unfortunately, one can not depend on the occurrence of fever to fight tumors, thus, artificial means of creating fever or heat were sought. Initially, bacterial toxins which induced fever were used in 1893 by Coley [3]. The discovery of ionizing radiation in 1895 led to the use of radiation as a treatment modality for cancer. The advantage of radiation over fever was the good reproducibility. Each patient responded differently to a toxin and, thus, the response was unpredictable with fever. This effect was not seen with radiation.

Several investigators studied the effect of heat on animal tumors in the late 1920's. High frequency currents were used on mouse tumors in 1928 [4]. Investigators combined heat and radiation as a treatment modality since better tumor
response was observed. Ultrasound was first introduced by Freundlich et al. 1932 [5] to heat tumors. Due to the ability of ultrasound to heat deep tumors and because ultrasound energy could be applied locally without destroying the surrounding tissue, it became widely used. In 1942 Lynn et al. reported that ultrasound was used to necrose tissue by using high intensity dosages [6]. Until the early seventies both the low-temperature technique and the tissue-necrosis technique were used. In the early 70's it was discovered that cessation of cell division was attained if the cells were heated to about 43 °C for 30-60 min [7]. A new modality was defined, known as hyperthermia, which became the most popular method utilizing elevated temperatures for therapy for at least two decades. The success of this modality depends solely on the accurate measurement of temperature which, in turn, requires the use of an invasive thermometry system. Also, the perfusion which is variable, might create cold spots at some sites. Some researchers chose the tissue necrosis technique (or ultrasonic surgery) over hyperthermia because of these disadvantages.

The main problems of ultrasonic surgery were (a) the size of the necrosed volume was not predicted adequately, and (b) the lack of an imaging system that could provide good contrast between necrosed tissue and normal tissue was not available. In the early 1980's [8] and [9] developed theoretical models for predicting intensity thresholds for tissue necrosis. In the beginning of the 1990's Hynynen et al. [10] developed a system that applies ultrasound inside an MRI scanner. Thus, the necrosed tissue volume can be visually monitored and controlled. These ideas further
encouraged the application of ultrasonic surgery for the treatment of cancer.

Several papers were published in the area of surgery since the publication of
the first paper [6]. Table 1 lists the most important papers in ultrasonic surgery in
chronological order. The table gives information on the type of tissue or tumor used,
the type of animal, and the key results or conclusions. The studies mainly cover
applications for the central nervous system, eye, liver, kidney, prostate, spinal cord,
muscle and tumors.

The aim of this study was to evaluate the physical parameters that determine
the necrotic tissue volume during high-intensity ultrasound using a numerical model.
The model uses the concept of thermal dose as the tool for the prediction. The
bioheat transfer equation is used to calculate the temperature induced by simulated
ultrasound field and then, using the formulation of Sapareto and Dewey in 1984 [11],
the thermal dose is found from the temperature history. By knowing the thermal dose
threshold for tissue necrosis, the boundary of the necrosed volume can be determined,
and, thus the size and the shape of the thermal lesions become known.

In this study high-intensity ultrasound applied by a spherically focussed
transducer is assumed. Deep-seated targets are of primary interest. The thermal
properties of tissues are assumed to be spatially homogeneous. Experimental data
obtained using methods described in this document or by other authors are used to test
the accuracy of the theoretical approaches.

The necrosed volume as a function of sonication conditions (pulse duration,
TABLE 1

MOST IMPORTANT PUBLICATIONS IN ULTRASONIC SURGERY.

<table>
<thead>
<tr>
<th>AUTHOR (S) AND REFERENCE</th>
<th>YEAR</th>
<th>ANIMAL OR TISSUE</th>
<th>IMPORTANT RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballantine H. et al., [13]</td>
<td>1956</td>
<td>Cat brain and mouse spinal cords.</td>
<td>Lesion size at different number of pulses. Peak intensity measured at the center of the lesion.</td>
</tr>
<tr>
<td>Curtis J. et al., [17]</td>
<td>1963</td>
<td>Mouse liver.</td>
<td>Infarction of liver for intensities higher than 10 W/cm² (5 min).</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Tissue Type</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------</td>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Young G. and Lele P., [18]</td>
<td>1964</td>
<td>Rabbit brain.</td>
<td>Lesion size vs. ultrasonic dosage (0.5 and 2 s pulses) at different intensities.</td>
</tr>
<tr>
<td>Taylor K. and Connoly C., [21]</td>
<td>1969</td>
<td>Cat liver.</td>
<td>Tissue damage for intensities higher than 10 W/cm².</td>
</tr>
<tr>
<td>Dunn F. et al., [26]</td>
<td>1975</td>
<td>Brain.</td>
<td>Intensity threshold vs. pulse duration at different frequencies.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Organ/Tissue</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Johnston R. and Dunn F.</td>
<td>1976</td>
<td>Cat brain.</td>
<td>Lesion volume vs. absorbed energy per unit volume (at different intensities). Lesion volume vs. pulse duration (at different intensities).</td>
</tr>
<tr>
<td>Frizzell L. et al.</td>
<td>1977</td>
<td>Rabbit kidney, liver, and testicle</td>
<td>Intensity threshold vs. pulse duration at 2 and 6 MHz (frequency independent threshold).</td>
</tr>
<tr>
<td>Lizzi F. et al.</td>
<td>1978</td>
<td>Rabbit eye.</td>
<td>Ophthalmoscopic examinations revealed cataract production due to high intensity ultrasound. Pulse duration needed to cause cataract is given in the range of 35 ms to 5 s.</td>
</tr>
<tr>
<td>Fry F. and Johnson L.</td>
<td>1978</td>
<td>Hamster tumors.</td>
<td>Matrix of points was sonicated with 7 s pulses (spaced 2 mm). Ultrasound combined with chemotherapy.</td>
</tr>
<tr>
<td>Smachlo K. et al.</td>
<td>1979</td>
<td>Hamster fibrosarcoma.</td>
<td>Treatment of tumors with high intensity ultrasound show no indication of metastasis.</td>
</tr>
<tr>
<td>Carstensen F. et al.</td>
<td>1981</td>
<td>Bovine liver.</td>
<td>Theoretical intensity threshold vs. pulse duration (2.25 MHz and 4 MHz). Experimental verification of model.</td>
</tr>
<tr>
<td>Goss A. and Fry F.</td>
<td>1982</td>
<td>Subdermally implanted Yoshida sarcoma in rats.</td>
<td>Tumor volume decreased compared to control.</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Tissue/Condition</td>
<td>Findings</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lizzi L. et al.,</td>
<td>1984</td>
<td>Ocular tissue.</td>
<td>Temperature prediction model. Intensity vs. pulse duration threshold (experimental verification in rabbit). Lesion diameter vs. pulse duration.</td>
</tr>
<tr>
<td>Borrelli M. et al.,</td>
<td>1986</td>
<td>Mouse spinal cord.</td>
<td>Irreversible hind limb paralysis and sensation loss were associated with altered morphology in the ventral and dorsal half of the spinal cord.</td>
</tr>
<tr>
<td>Coleman D. et al.,</td>
<td>1986</td>
<td>Human refractory glaucoma.</td>
<td>70 % of patients treated with ultrasound had intraocular pressure reduction to 25 mm Hg in one year after the treatment.</td>
</tr>
<tr>
<td>Frizzell L.,</td>
<td>1988</td>
<td>Cat liver.</td>
<td>Intensity vs. pulse duration threshold.</td>
</tr>
<tr>
<td>ter Haar G. et al.,</td>
<td>1989</td>
<td>Pig liver.</td>
<td>Lesions were tolerated without evidence of hemorrhage or infection.</td>
</tr>
<tr>
<td>Moore W. et al.,</td>
<td>1989</td>
<td>Hepatoma in rats.</td>
<td>The volume decreased in groups treated with chemotherapy and high intensity ultrasound.</td>
</tr>
<tr>
<td>ter Haar G. et al.,</td>
<td>1991</td>
<td>Rat liver tumors.</td>
<td>When tumor was covered entirely, no evidence of tumor growth was observed.</td>
</tr>
<tr>
<td>Yang R. et al.,</td>
<td>1992</td>
<td>Subcutaneous murine neuroblastoma (mice).</td>
<td>High intensity ultrasound and chemotherapy gave best results (number of survivors was the highest).</td>
</tr>
</tbody>
</table>

Susani M. et al., [45] 1993  Human prostate  Histological findings showed consistent coagulative necrosis with sharp margins to normal tissue.


Damianou C. and Hynynen K., [48] 1993  Dog and rabbit thigh.  Lesion size vs. power, pulse duration, frequency, F-number (theoretical). Intensity threshold vs. pulse duration (theoretical).

Acoustical power, transducer parameters (frequency, F-number = radius of curvature/transducer diameter) and tissue parameters (attenuation, perfusion rate) is found. The problem of near-field heating, a problem of tissue damage due to the application of multiple pulses during hyperthermic application is studied. A parametric study is performed to select sonication (pulse duration, delay between pulses), and transducer (frequency, F-number) parameters that minimize near-field heating. The problem of near-field heating which occurs during traditional ultrasound hyperthermia, might also appear during ultrasonic surgery, and thus, the same
approaches can be used to evaluate and correct the problem. The last theoretical study is associated with the overlaying tissue damage when surgery is applied to highly-perfused tissue seated 1.5 cm deep. The same parameters as in the previous studies are considered for minimizing damage of the surrounding tissues.

Experiments were conducted to verify the theoretical studies. MRI (Magnetic Resonance Imaging) was used to monitor tissue changes due to the heating of ultrasound. The relationship between the MR signal intensity and temperature is introduced for rabbit and dog tissues in vitro.

The theoretical and experimental approaches of this document are applied to biological tissues. In order to apply the same approaches for tumors, one has to take into account the differences in acoustical and thermal properties of tumors compared with biological tissues.
1.1 Basic quantities in ultrasound.

The explanations of the basic quantities used are summarized from [49], [50]. These quantities will be very useful in understanding later the thermal effects of ultrasound.

The displacement amplitude \( u \) of a particle in simple harmonic motion from its rest position is given by

\[
\mathcal{u} = u_0 \sin(\omega t - \phi),
\]

(1)

where \( u_0 \) is the peak displacement, \( \omega \) is the angular frequency, \( t \) is the time and \( \phi \) is the phase. The particle displacement repeats itself with a certain time interval, the so called period of motion \( T \) where \( T \) is the reciprocal of the frequency \( f \).
The particle velocity \( v \), which is the rate of change of displacement, is given by

\[
v = \frac{du}{dt} = u_0 \omega \cos(\omega t - \phi). \tag{3}
\]

Similarly, the particle acceleration \( a \) is the rate of change of velocity and is given by

\[
a = \frac{dv}{dt} = -u_0 \omega^2 \sin(\omega t - \phi) = -\omega^2 u, \tag{4}
\]

which means that the acceleration is proportional to, but in opposite direction of the particle displacement. The wavelength \( \lambda \) is the minimum distance between points with the same particle displacement. The wavelength is related to frequency by

\[
c = \lambda f, \tag{5}
\]

where \( c \) is the propagation velocity. The propagation velocity relates the second
spatial derivative of particle displacement with the second time derivative of the displacement in the standard wave propagation equation or:

\[
\frac{\partial^2 u}{\partial x^2} = \frac{1}{c^2} \frac{\partial^2 u}{\partial t^2},
\]

(6)

The solution of the above equation gives the particle displacement with respect to time and the distance x by

\[u(x,t) = u_0 \sin \omega (t - x/c).\]

(7)

The propagation velocity is given in terms of physical parameters by

\[c = \sqrt{\frac{K}{\rho}},\]

(8)

where K is the bulk modulus of the medium (N/m²) and ρ is the density of the medium. Thus, the propagation velocity is strictly dependent on the properties of the medium. By knowing the frequency and the propagation velocity of the medium, the wavelength can be found. The wavelength is a very important parameter because it
determines the shape of the power field. Air has lower propagation velocity compared to solids and liquids because the bulk modulus is lower. Aluminum, an example of a solid, has the highest propagation velocity (highest bulk modulus). Water has an intermediate value. Soft tissues have values similar to water, except for lung which has the lowest (due to air spaces). Bone has the highest propagation velocity (highest bulk modulus). Table 1.1 gives some typical values of propagation velocities of biological tissues.

**TABLE 1.1**

**PROPAGATION VELOCITIES OF SOME BIOLOGICAL TISSUES [50].**

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Propagation velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>1500-3700</td>
</tr>
<tr>
<td>Tendon</td>
<td>1750</td>
</tr>
<tr>
<td>Kidney</td>
<td>1564-1640</td>
</tr>
<tr>
<td>Liver</td>
<td>1540-1640</td>
</tr>
<tr>
<td>Muscle</td>
<td>1508-1630</td>
</tr>
<tr>
<td>Testis</td>
<td>1595</td>
</tr>
<tr>
<td>Brain</td>
<td>1516-1575</td>
</tr>
<tr>
<td>Skin</td>
<td>1498</td>
</tr>
<tr>
<td>Fat</td>
<td>1400-1490</td>
</tr>
<tr>
<td>Lung</td>
<td>470-658</td>
</tr>
</tbody>
</table>
The compressive force $F_x$ at distance $x$ is given by Hooke's law

$$F_x = -K A \frac{du}{dx},$$

where $A$ is the cross-sectional area and $du/dx$ is the longitudinal strain. The pressure then is given by

$$\frac{p}{A} = -K \frac{du}{dx} = -\rho c^2 \frac{du}{dx} = \rho c u \omega \cos(\omega t - \omega x/c) = \rho cv.$$

A very important quantity in ultrasound is the acoustic impedance. The acoustic impedance is defined as the ratio of pressure and particle velocity.

$$Z = \frac{p}{v} = \frac{\rho cv}{v} = \rho c.$$

Thus, the acoustic impedance depends on the medium. The concept of impedance can be better understood by considering analogous quantities from electricity. The pressure is analogous to the voltage, the particle velocity is analogous to the current and the acoustic impedance is analogous to the electrical impedance. Table 1.2 shows
typical values of impedances in tissue. Most tissues have an acoustic impedance similar to water \((1.5 \times 10^6 \text{ kgm}^2\text{s}^{-1})\), except for lung which has the lowest value (lowest propagation velocity) and bone which has the highest (highest propagation velocity).

The acoustic impedance is important because its value determines the amount of reflection at the interface of two media of different acoustic properties. Fig 1.1 shows that the incident wave is reflected and partially transmitted at the interface. By using

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Acoustic impedance ((10^6 \text{ kgm}^2\text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>3.75-7.38</td>
</tr>
<tr>
<td>Tendon</td>
<td>-</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.62-1.71</td>
</tr>
<tr>
<td>Liver</td>
<td>1.7-1.74</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.61-2.07</td>
</tr>
<tr>
<td>Testis</td>
<td>-</td>
</tr>
<tr>
<td>Brain</td>
<td>1.56-1.62</td>
</tr>
<tr>
<td>Skin</td>
<td>1.8</td>
</tr>
<tr>
<td>Fat</td>
<td>1.29-1.37</td>
</tr>
<tr>
<td>Lung</td>
<td>0.19-0.26</td>
</tr>
</tbody>
</table>
the fact that the pressure is continuous, the following expression is derived relating the ratio of incident and reflected pressure with respect to the acoustical impedances (the derivation can be found in [49]).

\[
\frac{p_r}{p_i} = \frac{Z_2 \cos \theta_i - Z_1 \cos \theta_t}{Z_2 \cos \theta_i + Z_1 \cos \theta_t},
\]

(12)

where the subscript \( r \) denotes reflection and the subscript \( i \) denotes incidence.

Fig 1.1 Illustration of wave reflection and transmission at a plane interface between two media.
Now, considering normal incidence ($\theta_i=\theta_r=0^\circ$) then the expression is simplified to

\[ \frac{p_r}{p_i} = \frac{Z_2 - Z_1}{Z_2 + Z_1}. \]  

(13)

There are two important cases to be considered:

a) $Z_1 = Z_2$ then $p_r/p_i \rightarrow 0$. This means that the reflected pressure tends to zero. This is essentially what happens when the wave goes from soft tissue to soft tissue.

b) When $Z_2 >> Z_1$ then $p_r/p_i \rightarrow 1$. Therefore, all the pressure is reflected. This result is seen when ultrasound travels from soft tissue to bone interface.

The total energy of a particle is the sum of the kinetic energy (K.E.) and the potential energy (P.E.). At the initial position the particle has only K.E., therefore, the energy is given by

\[ e = \frac{1}{2} m v_0^2. \]  

(14)

The total energy is the sum of the energies of all the particles and thus the energy per volume is given by

\[ E = \frac{1}{2} \rho v_0^2. \]  

(15)
The intensity $I$ is the power per unit area and is given by

$$I = \frac{1}{2} \rho c v_0^2 \left( \frac{\rho c v_0}{2pc} \right)^2 = \frac{p_0^2}{2Z}. \quad (16)$$

Thus, the intensity depends on the square of the pressure amplitude $p_0$ and is inversely proportional to the impedance. In a real medium, the ultrasound is attenuated according to an exponential law. For the plane wave case, the intensity as a function of depth in tissue is given by

$$I(x) = I(0) e^{-2\mu x}, \quad (17)$$

where $I(x)$ is the intensity at depth $x$, $I(0)$ is the intensity at the tissue interface, $\mu$ is the attenuation coefficient per unit length, and $x$ is the depth.

For a continuous, single frequency, plane ultrasound wave (and neglecting the shear viscosity) the temporal average absorbed power density $<q>$ is given by

$$<q> = 2\alpha I, \quad (18)$$

where $\alpha$ is the absorption coefficient (Np/m). The above relationship is valid also at
the focus of a focussed transducer. The absorbed power intensity is an important quantity because it is the primary factor determining the temperature elevation in tissue.

Two terms that are often confused are attenuation and absorption. Attenuation is due to absorption (energy loss due to heat conversion), scattering, and reflection. There are two theories to explain absorption. The first one is the classical which is based on viscosity. Due to shear forces in the medium there is time lag between the pressure amplitude and the particle velocity which results in energy loss for every cycle. However, this theory predicts a quadratic relationship of the absorption coefficient with frequency which has not been seen in tissues at low frequencies [50]. The additional theory of relaxation was proposed which explains the linear dependence of the absorption coefficient with frequency. During the compressive part of the cycle the acoustical energy is converted to kinetic energy, carried by the tissue's molecules. This energy is redistributed in the system in the form of lattice vibrational energy, translational energy, and molecular vibrational energy. If there were no coupling between these types of energy, all the energy would be returned during the expansion cycle and the absorption would be zero. However, due to coupling between the energy compartments there is a finite time associated with the redistribution of energy. Thus, the returned energy is in phase with the transmitted energy and this will result in absorption.

Based on experimental observations, the absorption coefficient (Np/m) is given
as a function of frequency by

\[ \alpha = \alpha_0 f^m, \]  

(19)

where \( \alpha_0 \) is the absorption coefficient (Np/m/MHz) and \( m \) is a constant. Both \( \alpha_0 \) and \( m \) are dependent on the tissue type. Experimentally \( m \) was found to be between 1 and 1.3 [51], [52]. Table 1.3 shows values of attenuation and absorption for some biological tissues. For some tissue types a range of values is given, since there are differences in the results from author to author. The absorption values as expected are smaller than the attenuation values.

### 1.2 Power field calculation.

The numerical calculation of the power field is based on the solution of the Sommerfield integral [53], which relates the velocity potential \( \Psi \) with the normal velocity \( u \) by the following equation

\[ \Psi = \int_A \frac{ue^{-js}}{2\pi s} dA, \]  

(20)
TABLE 1.3
ATTENUATION AND ABSORPTION FOR BIOLOGICAL TISSUE [50].

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Attenuation (Np/m/MHz)</th>
<th>Absorption (Np/m/MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>4-29</td>
<td>1.2-6.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>3-10</td>
<td>3.3</td>
</tr>
<tr>
<td>Liver</td>
<td>3.2-18</td>
<td>2.3-3.2</td>
</tr>
<tr>
<td>Lung</td>
<td>4.3-480</td>
<td>7</td>
</tr>
<tr>
<td>Muscle</td>
<td>4.4-15</td>
<td>2-11</td>
</tr>
<tr>
<td>Bone</td>
<td>150-350</td>
<td>-</td>
</tr>
</tbody>
</table>

where \( k \) is the wave number \((2\pi/\lambda)\), \( u \) is the normal velocity and \( s \) is the distance from a source point on the surface element \( dA \) on the transducer to a field point where \( \Psi \) is to be evaluated. The assumptions governing the solution of the above integral are:

a) the amplitude is assumed small so that non-linear effects do not play any role.

b) the surface \( S \) is slightly curved so that secondary diffraction due to the radiation of waves of the various transducer elements is neglected.
c) the attenuation is entirely due to absorption (ie. where attenuation is mentioned absorption is implied).

The normal velocity is represented by

$$u = u_0 e^{j\omega t},$$

(21)

where $u_0$ is a constant. The acoustic pressure is represented by

$$p = \rho \frac{d \Psi}{dt} = j\omega \Psi = jkc \Psi.$$  (22)

Fig 1.2 shows the geometrical arrangement of the transducer with the various distances, where $z$ is the distance in the axial direction from the origin to the field point $Q$, $r$ is the distance from the central axis to point $Q$ in the radial direction, $R$ is the radius of curvature, $D$ is the diameter of the transducer, $h$ is the depth of the concave surface, and $\delta$ is the angle between the line connecting the focus with the transducer boundary and the line of the central axis. These quantities are related by the following expressions

$$\frac{D}{2} = R \sin \delta,$$  (23)
Fig. 1.2 Geometry of spherically focussed transducer.

\[ h = R - R \cos \delta, \]  \hspace{1cm} (24)

\[ S = 2\pi Rh, \]  \hspace{1cm} (25)

where \( S \) is the transducer's surface area. Then, the emmitance \( e_I \) (W/cm\(^2\)) of the transducer may be written as

\[ e_I = P/S, \]  \hspace{1cm} (26)

where \( P \) is the total acoustical power.
1.2.1 Simplified model.

To simplify calculations, only those elements of area on the transducer over which \( s \) is constant are considered. This assumption reduces the integral to a one-dimensional integral. Another simplification used is associated with the effective attenuation distance \( s' \). In a weakly attenuating medium, the effect of attenuation is approximated using eq. 17. In this model \( s' \) is assumed as the distance from the water-tissue interface to the point of interest (this assumption is true for a planar transducer, good approximation for high F-number transducers and a weaker approximation for low F-number transducers) [53]. Because of the above simplifications the integral is reduced to

\[
\Psi(s) = \frac{\mu}{2\pi} e^{-\mu s'} \sum_{m=1}^{M} (e^{-i\beta_m A_m}/s_m),
\]

(27)

where \( A_m \) is the area of the \( m \)th annular strip and \( M \) is the number of strips in which the transducer is divided.

A computer program calculating the power field using the above technique [53] was used. The program requires information such as the frequency, radius of curvature, diameter of the transducer, acoustical power, attenuation coefficient,
distance of transducer from the skin (controls depth of focus in the tissue). The dimensions of the field size can also be specified by the user as well as the spatial step.

1.2.2 Parallel flat plane interface model.

It was stated in section 1.1, that when sound waves cross the interface between two mediums of different acoustical properties, refraction and reflection take place. The angle of the transmitted wave depends on the angle of incidence and the propagation velocities of sound in the media as described by Snell's law. A model was developed [54], which incorporates the refraction of the wave at the interface. The model calculates the acoustic pressure in the second medium due to a point source located in the first medium. The problem was simplified by assuming a plane interface between the media. After a rigorous analysis, the pressure in the second medium is calculated. The ray path length, transmission coefficient, and amplitude factor are determined from the angle of incident. The model calculates the acoustic pressure in a given medium for the general case of n media and n-1 interfaces. The above idea was applied for the case of a transducer by dividing the transducer into small elements (point sources). The contribution of each element was added by using Huygen's principle [54]. A program using this technique was used to verify the accuracy of the simulations.
1.3 Temperature simulations

The temperature vs. time history was obtained by solving numerically the bioheat equation proposed by Pennes [55]. The explicit form of this equation is given by

\[ \rho_f c_f \frac{\partial T}{\partial t} = k \nabla^2 T - w_b c_b (T - T_a) + Q_p \]  

where \( \rho_f \) is the density of the tissue, \( c_f \) is the specific heat of the tissue, \( T \) is the temperature of the tissue, \( t \) is the time, \( w_b \) is the blood perfusion rate, \( c_b \) is the specific heat of the blood, \( T_a \) is the arterial blood temperature, \( k \) is the thermal conductivity of the tissue, and \( Q_p \) is the ultrasonic absorbed power density. The first term in the above equation represents the temperature rise with respect to time, the second term represents the conduction effect which tends to decrease the temperature, the third term represents the convection effect due to blood which decreases the temperature, and the fourth term represents the absorbed power density due to the ultrasonic source which increases the temperature. The blood perfusion is modelled as a uniform heat-sink with blood supplied by vessels into the tissue volume at body temperature \( T_a \) and exiting at a tissue temperature \( T \). The method of including the perfusion term is an engineering approximation, which is accurate at short pulse durations. All units and values of the above parameters are given in table 1.4.
### TABLE 1.4
PARAMETERS USED FOR THE TEMPERATURE VS. TIME SIMULATIONS.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_t$</td>
<td>Density of tissue</td>
<td>998</td>
<td>kg/m³</td>
</tr>
<tr>
<td>$c_t$</td>
<td>Specific heat of tissue</td>
<td>3770</td>
<td>J/kg°C</td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
<td>Variable</td>
<td>s</td>
</tr>
<tr>
<td>$T$</td>
<td>Temperature</td>
<td>Calculated</td>
<td>°C</td>
</tr>
<tr>
<td>$w_b$</td>
<td>Blood perfusion</td>
<td>Variable</td>
<td>kg/m³s</td>
</tr>
<tr>
<td>$c_b$</td>
<td>Specific heat of blood</td>
<td>3770</td>
<td>J/kg°C</td>
</tr>
<tr>
<td>$T_a$</td>
<td>Arterial Temperature</td>
<td>37</td>
<td>°C</td>
</tr>
<tr>
<td>$K$</td>
<td>Thermal conductivity of tissue</td>
<td>0.5</td>
<td>W/m°C</td>
</tr>
<tr>
<td>$Q_p$</td>
<td>Absorbed power density</td>
<td>Variable</td>
<td>W/m³</td>
</tr>
</tbody>
</table>
The bioheat transfer equation was solved by using the finite difference method. In order to demonstrate how the temperature is evaluated at a certain time the following subscripts were used: \( z \) is the variable representing distance in the axial direction, \( r \) is the variable representing distance in the radial direction, \( t \) is time, \( 1 \) is the adjacent spatial step in positive direction if used in conjunction with \( z \) or \( r \), otherwise new time step, and \(-1\) is the adjacent spatial step in negative direction used in conjunction with \( z \) or \( r \). The axial spatial step, radial spatial step, and time step are represented by \( \Delta z \), \( \Delta r \), and \( \Delta t \) respectively.

The time derivative of the temperature is given by a two point finite difference

\[
\frac{\partial T}{\partial t} = \frac{T_{zt+1} - T_{zt}}{\Delta t}. \tag{29}
\]

The Laplacian term of eq. 28 in cylindrical coordinates is given by

\[
\nabla^2 T = \frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} + \frac{\partial^2 T}{\partial z^2} + \frac{\partial^2 T}{\partial \theta^2}. \tag{30}
\]

Now, it is assumed that there is no variation of \( T \) with \( \theta \), thus, the last term in the Laplacian reduces to zero. The first term in the Laplacian is approximated by using a three point finite difference
The second term of the Laplacian is approximated by

$$\frac{\partial^2 T}{\partial r^2} = \frac{(T_{r+1} - 2T_r + T_{r-1})}{(\Delta r)^2}.$$  \hspace{1cm} (31)

Similarly, the third term of the Laplacian is given by

$$\frac{\partial^2 T}{\partial z^2} = \frac{(T_{z+1} - 2T_z + T_{z-1})}{(\Delta z)^2}.$$  \hspace{1cm} (33)

The bioheat equation is now written as

$$\rho c_p \frac{(T_{r+1} - T_r)}{\Delta t} = k \left[ \frac{(T_{r+1} - 2T_r + T_{r-1})}{(\Delta r)^2} + \frac{1}{r} \frac{(T_{r+1} - T_{r-1})}{(2\Delta r)} \right]$$

$$+ \frac{(T_{z+1} - 2T_z + T_{z-1})}{(\Delta z)^2} - w_c \phi_b(T_{\pi} - T_0) + Q_{\text{net}}.$$ \hspace{1cm} (34)
Thus, the temperature at the new time step is given by

\[
T_{\nu r+1} = T_{\nu r} + \frac{k\Delta t}{\rho c_f} \left[ \frac{(T_{\nu r+1}-2T_{\nu r}+T_{\nu r-1})}{(\Delta r)^2} + \frac{1}{r} \frac{(T_{\nu r+1}-T_{\nu r-1})}{(2\Delta r)} \right]
\]

\[
+ \frac{(T_{z+1r}-2T_{zr}+T_{z-1r})}{(\Delta z)^2} - w_g c_b \frac{\Delta t}{\rho c_f} \frac{(T_{\nu r}-T_0)}{\rho c_f} + \frac{\Delta t}{\rho c_f} Q_{\nu r}
\]

(35)

In the central axis (r=0) after using L'Hospital's rule the Laplacian is given by

\[
\nabla^2 T = 2 \frac{\partial^2 T}{\partial r^2} + \frac{\partial^2 T}{\partial z^2}
\]

(36)

and thus, the temperature is given by

\[
T_{\nu r+1} = T_{\nu r} + \frac{k\Delta t}{\rho c_f} \left[ \frac{(T_{\nu r+1}-2T_{\nu r}+T_{\nu r-1})}{(\Delta r)^2} \right]
\]

\[
+ \frac{(T_{z+1r}-2T_{zr}+T_{z-1r})}{(\Delta z)^2} - w_g c_b \frac{\Delta t}{\rho c_f} \frac{(T_{\nu r}-T_0)}{\rho c_f} + \frac{\Delta t}{\rho c_f} Q_{\nu r}
\]

(37)
1.4 Thermal dose calculations.

The effect of hyperthermia depends on the temperature and the duration of the heating. If a constant temperature could be maintained, then the duration of heating would be a reasonable way of expressing thermal dose, with units of time. In reality, however, a constant temperature is not maintained, so it is necessary to find a method of relating a treatment to an equivalent time at a specified reference temperature. A mathematical relation between time and temperature was described by Dewey [56] and given by

\[
T_1 = T_2 R^{(T_1 - T_2)},
\]

where \(T_1, T_2\) are temperatures at times \(t_1\) and \(t_2\) respectively, and \(R\) is a constant given by

\[
R = e^{-\frac{\Delta H}{2T(T-1)}},
\]

where \(\Delta H\) is the activation energy (cal/mol), \(T\) is the absolute temperature (°K) and the number 2 is the approximation to the universal gas constant (1.98 cal/°K-mol).

The calculation of the thermal dose for changing temperature exposure that can not be
described analytically, was done by using the technique suggested by Sapareto and Dewey [11]. The technique uses numerical integration to calculate the time that would give an equivalent thermal dose at a reference temperature under different temperature profiles. The reference temperature of 43 °C has been chosen since this is the standard temperature use in hyperthermic treatments. For any temperature profile the dose can be found by

\[ t_{43} = \sum_{t=0}^{t_{\text{final}}} R^{(43-T)} \Delta t, \quad (40) \]

where \( t_{43} \) is the equivalent time at 43 °C, \( T_i \) is the average temperature during \( \Delta t \). A value of \( R \) equal to 0.25 was chosen based on animal experiments for temperatures smaller than 43 °C and a value equal to 0.5 for temperatures higher than 43 °C [11].

The concept and unit of thermal dose referenced to a certain temperature is best illustrated by means of Fig 1.3. It is assumed that an idealized constant temperature of 43 °C is maintained for 120 s (thermal dose referenced at 43 °C is 2 min). Now, an ultrasound pulse of 5 s duration is applied. At sufficiently high power, this will cause temperature elevations higher than 43 °C. By using the function of eq. 40, a 2 min thermal dose referenced at 43 °C can be established. Thus, the same thermal dose of 2 min (as in the case of low power and long pulse duration) can be induced with high power and short duration pulse.
Fig 1.3 Demonstration of 2 min thermal dose at 43 °C using an idealized temperature profile and a typical temperature profile created using high intensity ultrasound.

1.5 Transducer arrangement

Unless otherwise specified, the modeling parameters utilized here are a transducer frequency of 1 MHz, a radius of curvature of 10 cm, a diameter of the transducer of 10 cm, while the transducer was located 5 cm from the water-tissue interface, and 100 pulses were applied (study of chapter 3). The low value of perfusion rate, 0.5 kg/m³/s, was used in the study of near-field heating (chapter 3) which minimizes the heat removed due to blood perfusion and as a result maximum
heating effects are considered. This low perfusion assumption provides a worst case scenario. The geometrical arrangement of the transducer is illustrated in Fig. 1.4.
1.6 Selection of decay time, spatial step, and time step.

Two sonication parameters that are very important in the case of near-field heating are the pulse duration and the delay between pulses. Pulse duration is the total time the ultrasound source is ON. The delay is the time between pulses and during this interval the ultrasound is OFF. Fig. 1.5 illustrates the definition of these parameters when multiple pulses are considered in the near-field (the pulse duration is 5 s and the delay between pulses is 5 s).

In the same figure (Fig. 1.5) the importance of using a decay time at the end of the sonications is illustrated. During the temperature decay the area under the temperature curve will contribute to the thermal dose. According to the thermal dose function, for temperatures higher than 43 °C, the dose is considerably higher. Thus, sufficient decay time should be provided to drop the temperature below 43 °C. Fig. 1.6 shows the effect of decay time on the thermal dose. When estimating the dose in the focus, 1 s seems to be adequate decay time (Fig 1.6.A) since the decay of temperature is fast. Fig 1.6.B shows the thermal dose vs. decay time for a location 1 cm away from the focus. The thermal dose reaches its maximum value (within 1 %) in 1 s. This fact is very important in the case of lesion size prediction (chapter 4) since the lesion size (as it will be seen later) is determined by the boundary of 240 equivalent min which is a few mms from the focus. Fig 1.6.C shows that a decay time of 200 s should be used when estimating the thermal dose in locations in the near-field.
Fig. 1.5 Definition of pulse duration, delay between pulses, and decay time.
Fig. 1.6 Thermal dose vs. decay time for a profile A) at the focus, B) field point 1 cm apart from the focus, C) point in the near-field.
when multiple pulses are applied. This is needed because at these locations the decay of the temperature is slow. From experience, the decay time is determined based on the amount of time the temperature is above 43°C. If for example the temperature was above 43°C for 200 s, then the decay time should be at least 50 % of 200 s (100 s). Field points closer to the focus require less decay time, because the temperature decays faster at these locations.

Another important parameter for the simulations is the spatial step. The error of the various terms of the Laplacian (eq. 30) depend on the spatial step. The lower the step, the better the accuracy of the derivatives involved (provided that the round-off error does not dominate). Fig. 1.7A illustrates the effect of spatial step on the temperature elevation (time step=0.05 s). The temperature elevation does not change much for a step of 0.25 mm or smaller. Fig. 1.7B shows that the thermal dose is stable for spatial steps of 0.25 mm or smaller. Using a smaller step increases the computation time and computer memory size, thus, the 0.25 mm step was used for the default simulations. The spatial step for other transducer geometries and frequency is determined based on the half-power width of the transducer. The smaller the half-power width, the smaller the spatial step needed to provide detailed sampling of the power field. Table 1.5 gives the spatial step and the time step for different half-power width ranges.

The time step affects the calculation of the time derivative of the temperature (eq. 29). The time step was determined based on Von Neuman analysis
Fig. 1.7 A) Temperature elevation vs. time for different spatial steps, B) Thermal dose vs. spatial step size. Time step=0.05 s.
TABLE 1.5

SPATIAL STEP AND TIME STEP AT DIFFERENT HALF-POWER WIDTH RANGES.

<table>
<thead>
<tr>
<th>Half-power width range (mm)</th>
<th>Spatial step size (mm)</th>
<th>Time step (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>1-4</td>
<td>0.25</td>
<td>0.05</td>
</tr>
<tr>
<td>4-10</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

[57]. Analysis of the bio-heat equation gives the following criterion for the time step based on the spatial step size ($\Delta z = \Delta t$):

\[
\Delta t \leq 2\left(\frac{12 \times k}{\rho \times c \times (\Delta z)^2} + \frac{w \times c_b}{\rho \times c_i}\right).
\]  

(41)

Now, since $c_b = c_i$ and the second term in the parenthesis is much smaller than the first (true for $\Delta z$ in the order of a few mms) then the criterion reduces to

\[
\Delta t \leq \frac{\rho \times c_i \times \Delta z^2}{6k}.
\]  

(42)
Thus, the higher the spatial step size, the higher the time step allowed. Also, the time step depends on the thermal properties of the tissue. Using the thermal properties of table 1.5 the time steps of 0.31, 0.07, and 0.012 s were found for spatial steps of 0.5, 0.25 and 0.1 mm respectively.

The choice of the time step was verified also numerically. Fig. 1.8A shows the temperature profiles for a 5 s pulse. The temperature profile for time steps 0.07 s or smaller, does not change a lot with time step. The time step has some effect on the decay part of the profile and no effect on the rising part. The thermal dose for time steps smaller than 0.07 s does not change (Fig. 1.8B). The time step of 0.05 s was used because it was easier to read the data files. The maximum time step is selected based on the spatial step. The time step for all the transducers of different half-power beam width was checked numerically and agreed with the time steps found analytically.

1.7 Dose vs. power relationship.

The relationship between thermal dose and acoustical power is useful for two applications. The first use is when the power that establishes 60 min at the focus is required (application of ultrasound for hyperthermic treatments-chapter 3). The second use is to find the power that establishes 240 min at the focus. The dose of 240 min, as it will be seen later, is the critical dose that causes necrosis (chapter 4). The
Fig. 1.8 A) Temperature elevation vs. time for different time steps, B) Thermal dose vs. time step.
logarithm of dose vs. power at the focus as shown in Fig. 1.9 (for 1 and 5 s pulse durations) was found to obey a linear relationship [58]. The slope varies with pulse duration, frequency, F-number, perfusion rate and attenuation coefficient. Only two points are needed in order to find the power $P$ that establishes a certain dose $d$ due to the linear relationship. Let $d_1$ and $d_2$ be two different doses at power levels $P_1$ and $P_2$. Then using the two slopes at points $(P_1, P_2)$ and $(P, P_1)$

$$\frac{\log(d_1)-\log(d_2)}{P_1-P_2} = \frac{\log(d)-\log(d_1)}{P-P_1},$$

and thus the power $P$ is given by

$$P = P_1 + \frac{\log(d)-\log(d_1)}{\log(d_1)-\log(d_2)}(P_1-P_2).$$

A typical example of calculating the power to establish a specified thermal dose is shown next. From Fig. 1.9, for a 1 s pulse duration at $P_1=30$ W, $\log(d_1)=0.2$ and for $P_2=50$ W, $\log(d_2)=2.8$. Then, the power $P$ required to establish a dose of 60 min may be calculated from eq. 44 as

$$P = 30 + \frac{(1.778-0.2)}{(0.2-2.8)} \times (30-50) = 42.1 W.$$
Fig. 1.9 Log (dose) vs. power for 1 and 5 s pulses.

1.8 Computer program.

A computer program was written in FORTRAN using the compiler WATCOM 77. The program is run in an IBM compatible personal computer. The program calculates the temperature vs. time profile based on the power distribution obtained using the methods of section 1.2. The temperature when multiples pulses are applied can also be calculated. The pulse duration, delay between pulses, decay time, and time step are specified by the user. The user can also specify the tissue baseline
temperature and the perfusion rate. The thermal properties of the tissue such as conductivity, specific heat of tissue, density of tissue, specific heat of blood, and arterial temperature can be changed by editing the program. The temperature at any field point can be calculated. Based on the temperature vs. time history the thermal dose referenced at any temperature can be calculated using the methods of section 1.4. Based on the thermal dose distribution, the lesion size can be calculated by using the thermal dose of necrosis of the tissue. The thermal dose of necrosis of the tissue can be specified by the user.
CHAPTER 2

EXPERIMENTAL SETUP

Experiments were carried out to investigate how well the simulations predicted actual measurements. The experiments were performed on greyhound dogs and rabbits thigh muscle in vivo. During the experiment the dogs were kept under continuous anesthesia (Halothane). The dogs weighed about 30 kg and the rabbits 3-4 kg. The rabbits were anesthetized by a mix of 500 mg Ketamine, 100 mg Rompun and 20 mg Acepromazine, at a dose of 1mg/kg. The animal's thigh muscle was shaved and cleaned with soap to improve coupling. The thigh was placed above an acoustical window made of thin mylar (thickness=75 μm). Water was placed between the thigh and the acoustical window to improve coupling.

2.1 Sonication system

The ultrasound equipment and thermometry system for this setup is shown in Fig 2.1. The ultrasound field was generated by a single, spherically focused, air backed transducer. Two different transducers with different radii of curvatures (8 and 10 cm) were used. The diameter of both transducers used was 10 cm. The transducer was placed in a water bath which was degassed to remove air bubbles.
Fig. 2.1 Experimental setup.
The distance from the transducer to the skin was varied so that different depths in tissue were achieved. The radio frequency (RF) signal feeding the transducer was obtained from a function generator (Stanford Research System, Sunnyvalle, CA, model DS 345). The signal was amplified by an RF amplifier (ENI Inc., Rochester, NY, model A500 or model A150). The electrical impedance of the transducer was matched to the output impedance of the amplifier (50 Ω) by an external LC matching network. The forward and reflected electrical power was measured using a digital power meter (Hewlett-Packard, model 438A) and a dual directional coupler (Werlatone, model C2625). The frequency, pulse duration, delay between pulses and the RF power were controlled by an IBM-compatible computer using an Intel 80386 CPU. The transducer was moved by stepper motors in the X, Y, and Z directions. The motors were computer controlled via a stepper motor drive interface. The XYZ positioner consists of two different positioners. One positioner controls the XY movements and the other the Z movement. The XY positioner was an open free table by Daedal unit with a resolution of a 2000 steps per mm. The Z-positioner was driven by a Bordine stepper motor with a resolution of 400 steps per mm. The system is described in detail in [59].

2.2 Thermometry system.

Two different temperature systems were used. The temperature in the first
system was monitored by using a seven sensor manganin-constantan thermocouple probe in fused silica tubing [60]. This system was used to measure temperature in the near-field at multiple depths in tissue. The probe contained seven separate thermocouples, with junctions spaced at 1 cm intervals. The first thermocouple sensor was placed a few mms inside the skin. The probe was oriented parallel to the beam so as to minimize the temperature measurement artifact caused by the interaction between the thermocouple and the ultrasound beam. The thermocouple voltages were measured in sequence by a digital voltmeter (HP 3456A) via a data acquisition system (HP 3497A) and converted to temperatures by a computer (HP 9836). The temperatures were sampled every 10 s.

The second system reads temperature from a single probe by using a commercial temperature acquisition system (Isotherm-X, Columbus Instruments) [59]. A single sensor thermocouple probe (wire diameter = 50 μm) at the acoustical focus was used for establishing the thermal dose at the focus. Based on the experimental temperature profile and by using the same formulation of the thermal dose in section 1.4, the thermal dose was measured. The Isotherm-X temperature unit was controlled by a PC using an RS 232 interface. The system was electrically isolated with a leakage current smaller than 10 μA. The measuring rate varied from 5 to 10 readings per second depending on the computer language used. Based on manufacturer's data the accuracy of the measurement was 0.1 °C and the resolution was 0.015 °C. Data from thermocouples are read in the form of two bytes of data. The data was then
converted to temperature by comparing data with a linearizing table.

The thermocouples were made in house, using manganin and constantan (California fine wire company, Grover city, CA). The two materials in the form of 50 μm diameter wires (electrically insulated) are twisted together and soldered to form the thermocouple junction. The junction is formed about 10 cm from the end of the wire so that an optical fiber can be connected to the end. The optical fiber is used to assist the insertion of the thermocouple through the catheter. The two other open ends are connected to the standard Baily miniature connector (Omega, Stamford, CT). The stress in the connection is reduced by applying epoxy inside the connector.

2.3 Locating of thermocouple.

The thermocouple location is found by moving the transducer around and sonicating until the location of maximum temperature rise is found (for detailed description the reader may consult [59]). The distance from the transducer to the skin is varied until the focus is placed at the same depth as the thermocouple junction. This requires knowledge of the thermocouple depth in tissue and the transducer focal length. Initially a square pattern of considerably large area is selected to be scanned by the transducer. A large step size is used initially (larger than the half-power width of the transducer). Based on the scan size and the step size a certain number of pulses are applied. For example, a 10x10 mm² area with a 1 mm step is scanned with 11x11
(121) pulses. At each point two temperatures are taken. One reading is before ultrasound is turned ON and the second is taken slightly before ultrasound is turned OFF. The difference between the two readings is a measure of how close the sonicated point is to the thermocouple. The higher the difference the closer the sonication and the thermocouple are. Since the locating time depends on the scan size and step size, the transducer center of curvature is placed as near to the thermocouple as one can possibly accomplish based on hand measurements. When the location of maximum temperature difference is detected, the transducer is automatically positioned to that location. The procedure is repeated with smaller scan and step sizes, until a scan area is found that the temperature rise does not change significantly at the subsequent sonications. This means that the step size is small enough compared to the size of the focal region. After locating in the XY plane the transducer is moved in small steps in the Z direction until a maximum temperature difference is found as a function of depth in tissue. This is needed because the focus of the transducer might not be exactly in the plane of the thermocouple.

2.4 Ultrasound power measurement.

The acoustical power vs. the net electrical power (forward minus reflected) was measured using the force technique with a lab balance (Mettler, Hightstown, NJ, model AE160) as the force detector. The radiation force was detected using an
absorbing brush target. The target was manufactured by placing 9 cm long plastic fibers made of polystyrene (Magnolia Brush, MARS Inc., Clarkville, TX) on a silicone rubber base. The target was hung from the balance and the beam was aimed vertically to the target. The whole setup was immersed in a tank of degassed water. The measurement setup and computer control were developed earlier and described by [61]. Fig 2.2 shows how the transducer and target are immersed in the water tank. Fig 2.3 shows the block diagram of the force balance measurement. The force
Fig. 2.3 Force-balance measurement-block diagram.
balance setup was controlled by an HP computer (HP 98236) via an IEEE-488 interface. The computer also controls the sonication of the transducer. A signal generator (Wavetek, model 271) excited an amplifier (ENI Inc., Rochester, NY, Model A300) and through a matching network power is transmitted to the transducer. A dual directional coupler (Werlatone, model C2625) was inserted between the matching network and the amplifier which was connected to a power meter (HP, model 438A) to measure the net electrical power. The measurement was stored in the computer. The mass \( m_0 \) of the target was measured initially. Next the power was applied for 5 s and the new mass was sampled every 0.5 s. The average mass \( m_{\text{ave}} \) during the interval the ultrasound was ON was then calculated. The acoustic power \( P_A \) is given by

\[
P_A = (m_{\text{ave}} - m_0)gc, \tag{46}
\]

where \( g \) is the gravitational constant, and \( c \) is the speed of sound in water. Since \( c \) depends on the temperature, the value of \( c \) used, was determined based on the temperature of the bath. The transducer efficiency \( \eta \) is given in terms of the acoustical power \( P_A \) and the electrical power \( P_E \) by

\[
\eta = \frac{P_A}{P_E}. \tag{47}
\]
Fig 2.4 shows a typical graph of acoustical power vs. electrical power for a transducer that was used in the experiments. It is good practice to measure the efficiency of the transducer two or three times and average the results. Also, the efficiency should be measured occasionally so that any change in efficiency due to usage is known. Typically the efficiency of the transducers used in the experiments was about 50 %, while the variation from experiment to experiment was about 5 %.

Fig. 2.4 Typical graph of acoustical power vs. electrical power for a transducer used in the experiments (f=1.656 MHz, R=8 cm, D=10 cm).
CHAPTER 3

FOCAL SPACING AND NEAR-FIELD HEATING DURING PULSED HIGH TEMPERATURE ULTRASOUND THERAPY.

3.1 Introduction.

The traditional hyperthermic treatments have a thermal exposure goal of 30 to 60 min at 43 °C [7], [11]. However, due to local perfusion variations, cold spots are almost always observed. One way to minimize this effect is to monitor the temperature (invasively) and scale the power appropriately to obtain a more uniform temperature distribution [62]. Another method to reduce the effect of perfusion is to use short pulses of high power to deliver a therapeutic thermal dose [63]. This high temperature hyperthermia can be induced by using sharply focussed ultrasound beams and it has been shown to be perfusion insensitive [64], [65], [66], [67].

In order to avoid transient cavitation, the operating frequency must be above 1 MHz [68] and thus the focal size is small when sharply focussed transducers are used. As a result, multiple sonications are required to cover the whole target volume. Due to overlapping of the beam in some locations in front of the focus during multiple sonications, the temperature at these near-field locations could increase to a level that can cause tissue damage. The aim of this study was to quantify the required focal
spacing and to suggest sonication and transducer parameters that minimize the undesirable near-field heating. While most results presented are from computer simulations, some experimental data are given to demonstrate the degree of accuracy of the simulations.

3.2 Near-field dose calculation.

In order to cover a typical clinical target volume, multiple ultrasound pulses must be given at multiple locations. Although the temperature elevation in front of the focus during a short ultrasound burst is small, when applying multiple pulses a cumulative temperature elevation is induced. This temperature elevation causing tissue damage was observed using MRI [10]. Thus, tissue heating in front of the focus requires a careful study. During a clinical treatment, a tumor volume is sonicated by dividing the tumor into axially symmetric layers. The spacing between the layers is determined such that the resulting dose at any field point due to adjacent pulses is between 30 to 60 min. Within a certain layer, pulses are applied to cover the entire region with a dose between 30 to 60 min by selecting the spacing of the pulses appropriately. The problem of tissue heating in the near-field is illustrated by means of Fig. 3.1. In this figure the transducer is moved three times. The reader may note that in all transducer locations point A lies within the beam and thus, the temperature builds up. Point B is inside the beam once in this example and therefore it suffers less
heating. Generally, points in the central axis of the tissue volume, lie inside the beam more often. Considering the case of area 10x10 mm² treated with a 1 mm spacing, then 100 pulses are needed. To simplify computations, the temperature of a field point

Fig. 3.1 Illustration of near-field heating during pulsed high temperature hyperthermia.
in front of the focus is calculated by assuming that all the pulses (100) are applied to that particular point. This assumption allows utilization of cylindrical coordinates and thus, the speed of the calculations is enhanced. This assumption will give the worst case heating for that point. Only one pulse is used to normalize the thermal dose at the focus, because the dose contribution of the subsequent pulses is considered negligible at the focal location.

3.3 Simulation results.

In order to treat a large volume, multiple pulses are required. The locations of the pulses have to be close enough so that adequate thermal dose is delivered between the pulse locations in both the radial and the axial directions. Fig. 3.2 illustrates the thermal dose distribution induced by three different spacings in the axial direction. If the dose of 30 min at 43 °C is used as the minimum dose between the pulses, then the maximum spacing for different transducers can be calculated. A maximum dose of approximately 60 min is required. The spacing used for the dose calculations shown in Fig. 3.2A was 3 mm; it was too short because the maximum dose approached 70 min. The spacing of Fig. 3.2B was 5 mm, but it was too long because the dose dropped below 30 min at some locations. Fig 3.2C presents the results for a 4 mm spacing and demonstrates the correct spacing since the thermal dose was between 30-60 min.
Fig 3.2 The axial thermal dose distribution for two adjacent pulses for $f=1$ MHz, $R=10$ cm, $D=10$ cm, Pulse duration=1 s, Delay=20 s, Perfusion=0.5 kg/m$^3$/s. A) 3 mm spacing, B) 5 mm spacing, C) 4 mm spacing.
The spacing is a strong function of both F-number and frequency. Fig. 3.3 shows the spacing between pulses in the radial direction as a function of frequency and F-number for 1 and 5 s pulses for spherically curved transducers. Fig. 3.4 shows the corresponding plot in the axial direction.

To better understand how the spacing varies with frequency and F-number it is useful to look at the power density distribution for various frequencies and F-numbers in the axial direction. Fig 3.5A shows the power density distribution in the axial direction at different frequencies. The power field becomes narrower as the frequency increases. The power field becomes wider as the F-number is increased (Fig 3.5B). In Fig 3.5B the focus is kept at a depth of 5 cm in the tissue by varying the distance from the transducer to the tissue. From Fig 3.5 it is obvious that the spacing is increased as the F-number is increased, and decreased as the frequency is increased. The spacing also increases with the pulse duration simply because the thermal dose is higher for longer pulses. The same principle holds when considering spacing in the radial direction.

In Fig. 3.6 typical temperature vs. time profiles for two different locations are shown. The first case (Fig. 3.6A) is a profile obtained at the focus. The temperature rise is high and the decay fast. The reason the decay is fast is because the focus is at the highest temperature and, therefore, the conduction is much higher than any other location. The second case (Fig. 3.6B) corresponds to a field point 3 cm deep. The temperature elevation is small. The decay is much slower, since the
Fig. 3.3 The radial spacing vs. F-number at different frequencies. A) 1 s pulse, B) 5 s pulses. D=10 cm, Perfusion=0.5 kg/m$^3$/s.
Fig. 3.4 The axial spacing vs. F-number at different frequencies. A) 1 s pulse, B) 5 s pulses. D=10 cm, Perfusion=0.5 kg/m²/s.
Fig. 3.5 A) Power distribution at different frequencies (F-number = 1) in the axial direction.
B) Power distribution at different F-numbers (f = 1 MHz) in the axial direction.
Fig. 3.6 The temperature elevation as a function of time induced by an ultrasound pulse at A) the focus (5 cm deep), and B) in the near-field (3 cm deep).
thermal gradients are much smaller, and thus the rate of thermal conduction is reduced.

The effect of multiple sonications in the near-field is illustrated in Fig. 3.7. Three perfusion rates were examined with a pulse duration of 5 s and a delay between pulses of 10 s. The near-field temperature elevation is strongly dependent on the perfusion rate. The temperature reaches steady state in 200 s for the rate of 10 \( \text{kg/m}^3/\text{s} \), whereas for the low perfusion rate the temperature is still increasing at the end of the 1500 s sonications. As a result, the thermal dose decreases with increasing perfusion rate. The dose for the sonications in Fig. 3.7 for the \( 0.5 \text{ kg/m}^3/\text{s} \) rate is 24.4 min, and for the \( 10 \text{ kg/m}^3/\text{s} \) is 0.15 min.

The temperature elevation at steady state in the near-field can be found by setting the first term in the bioheat equation to zero since at steady state the temperature does not change with time. Also, the conduction term can be eliminated since the temperature gradients involved are low. Thus, the temperature in the near field is given by

\[
\omega_s c_p (T - T_o) = Q. \quad (48)
\]

What this equation implies is that for a given power density the temperature elevation is inversely proportional to the perfusion rate, i.e., the higher the perfusion rate the lower is the temperature elevation. Thus, by using short pulses the temperature at the
focus is independent of perfusion, but this is not the case in the near-field. However, if the near-field temperature is kept low, then the variation of temperature due to perfusion does not play any role.

The temperature elevation in the near-field can be reduced by allowing the temperature to decay more between the pulses. Fig. 3.8 illustrates the near-field temperature at a depth of 2 cm after 100 pulses of 5 s duration with different delays.

![Graph showing temperature vs time for different perfusion rates](image)

**Fig. 3.7** Temperature vs. time profiles for 0.5, 5, and 10 kg/m³/s perfusion rates. \( f = 1 \) MHz, \( R = 10 \) cm, \( D = 10 \) cm, \( P = 12.4 \) W (60 min at the focus), Pulse = 5 s (100 pulses), Delay = 10 s.
(1 to 30 s) between the pulses. The higher the delay between the pulses, the more heat is conducted away when the power is OFF. Therefore, the temperature at the subsequent pulse is lower than if a smaller delay between the pulses was used. For this type of pulse it would appear that a delay of 20 s is adequate to drop the temperature sufficiently low such that the thermal dose remains at safe levels. A steady state temperature is almost attained when the delay is 20 or 30 s. The

![Temperature vs. time profiles with different delays between pulses](image)

Fig. 3.8 Temperature vs. time profiles with different delays between pulses. Depth=2 cm, f=1 MHz, R=10 cm, D=10 cm, Power=12.4 W (60 min at the focus), Pulse=5 s (100 pulses), Perfusion=0.5 kg/m³/s.
temperature elevation reached with delays smaller than 20 s might cause excessive tissue damage. Fig. 3.9 shows the thermal dose at the depth of 3 cm as a function of delay between pulses. It appears that delays between 20-30 s would eliminate the potential of tissue damage in the near-field with frequency of 1 MHz, F-number 1 and 5 s pulse duration. Fig. 3.10 demonstrates the effect of the number of pulses on the thermal dose. This effect is an important factor with smaller focal zones which require smaller spacing between pulses. The number of pulses might increase also

![Diagram](image)

**Fig. 3.9** Thermal dose vs. delay between pulses at 3 cm depth. f=1 MHz, R=10 cm, D=10 cm, P=12.4 W (60 min at the focus), Pulse=5 s (100 pulses), Perfusion=0.5 kg/m^2/s.
when a larger area needs to be treated. It may be noted that the dose vs. number of pulses decreases with increasing the frequency. It appears that the dose increases linearly as a function of number of pulses. Fig. 3.11A demonstrates that shorter ultrasound pulses have smaller effect on the near-field heating than longer pulses. The downside of the shorter pulses is that the power required and thus, the focal

Fig. 3.10 Thermal dose vs. number of pulses at 3 cm depth. \( f = 1 \) MHz, \( R = 10 \) cm, \( D = 10 \) cm, Pulse = 1 s (100 pulses), Delay = 20 s, Perfusion = 0.5 kg/m³/s.
Fig. 3.11 A) Thermal dose vs. pulse duration at 1, 2, and 3 cm deep. 
f=1 MHz, R=10 cm, D=10 cm, Delay=20 s (100 pulses), 
Perfusion=0.5 kg/m³/s. B) Power to give 60 min at the focus vs. 
pulse duration. f= 1 MHz, R=10 cm, D=10 cm, Perfusion=0.5 
kg/m³/s.
intensity increases as a function of decreasing pulse duration (Fig. 3.11B). Tables 3.1 and 3.2 show the focal intensity and the total power, respectively, required to establish 60 min at the focus as a function of frequency and F-number for 1 and 5 s pulses. This result is significant since transient cavitation may be reached at high acoustic pressure (or intensity) values. The cavitation threshold for the pulse duration of 1 s and transducer with frequency of 1 MHz is about 1000 W/cm². Thus, the intensity required for 1 s pulse (950 W/cm²) is close to the cavitation threshold.

The thermal dose in the near-field was studied as a function of depth in tissue. It was found that the thermal dose did not change with depth provided that the power was scaled accordingly with depth in tissue (to establish 60 min dose at 43 °C at the focus). The thermal dose in the near-field was studied also as a function of attenuation coefficient (with thermal dose of 60 min at 43 °C at the focus). It was found that the thermal dose in the near-field increased with increasing attenuation coefficient. The thermal dose calculated with an attenuation coefficient of 5 Np/m/MHz was 38 % of the dose with 10 Np/m/MHz (2 cm from the focus).

The operating frequency has an impact on the shape of the focal zone and also on the attenuation of ultrasound. The effect of the frequency on the near-field heating has been illustrated in Fig. 3.12. The thermal dose distribution becomes narrower as the frequency increases. Also, the value of the thermal dose increases with frequency because the attenuation coefficient increases with frequency. The two effects are competing in the sense that the one tends to decrease the near-field heating and the
TABLE 3.1

THRESHOLD INTENSITY NEEDED TO DELIVER 60 MIN EQUIVALENT DOSE
AT 43 °C AT THE FOCUS.

Transducer diameter = 10 cm, depth in tissue = 5 cm, perfusion = 0.5 kg/m³/s.

a) Pulse = 1 s

<table>
<thead>
<tr>
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b) Pulse = 5 s

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<th>1.5</th>
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<td>405</td>
<td>305</td>
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<td>130</td>
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</tbody>
</table>
TABLE 3.2
APPLIED POWER (W) TO DELIVER 60 MIN EQUIVALENT DOSE AT 43 °C AT THE FOCUS.

Transducer diameter=10 cm, depth in tissue=5 cm, perfusion=0.5 kg/m³/s

a) Pulse=1 s

<table>
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<tr>
<th>Frequency (MHz)/F-number</th>
<th>Power (W)</th>
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</table>

b) Pulse=5 s

<table>
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<tr>
<th>Frequency (MHz)/F-number</th>
<th>Power (W)</th>
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<td>05.4</td>
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<td>2.0</td>
<td>05.6</td>
</tr>
</tbody>
</table>
other tends to increase it. The first effect seems to dominate, thus, the dose drops with increasing the frequency. It appears that the effect of frequency is minimal at distances longer than 2 cm in front of the focus. However, at deeper field points (closer to the focus), the dose decreases with increasing frequency. It is logical that the stronger the focusing i.e. the smaller the F-number the smaller the near-field heating. Fig. 3.13 indicates that F-number around 1.0 or smaller should be used in order to minimize the near-field heating of a 1 s pulse and a 20 s delay.

Fig. 3.12 Thermal dose vs. frequency at 1, 2, and 3 cm. R=10 cm, D=10 cm, Pulse=1 s (100 pulses), Delay=20 s, Perfusion=0.5 kg/m³/s.
3.4 In vivo experimental results.

A 10x10 mm² area of thigh muscle of a dog was sonicated using 132 pulses. The seven sensor thermocouple probe was placed in the center of the sonication area. The pulse length was 7 s and a power that gives 60 min at the focus was used. The delays of 30 s, 10 s, 20 s, and 5 s were used at this sequence. In all four cases, the same sonication area was used. Sufficient waiting time between each case was
provided, so that the same baseline temperature was attained.

In the simulations of the experiments the attenuation coefficient of 4.1 Np/m/MHz and the perfusion rate of 0.65 kg/m³/s were used. These values were measured for thigh muscles of similar greyhound dogs in separate experiments [69].

The experimental results from the dog's thigh are next presented. Temperature elevation profiles are shown in Fig. 3.14A for a 20 s delay between pulses. At the beginning the temperature rises with time until steady state conditions are reached. The profile at 3 cm deep has higher temperatures as predicted. Fig. 3.14B shows experimental and simulated temperature profiles at a 2 cm depth and with a delay of 20 s. The experimental and simulated temperature elevations are in close agreement.

Finally, Fig. 3.15A shows the experimental and the simulated steady state temperature in the near-field vs. depth in the tissue. The reader may note that the separation of simulated and experimental steady state temperatures increases close to the focus. This separation exists because the assumption used in the simulation of considering all the pulses in one location (in the near-field) is not accurate close to the focus. However, the agreement is good at the depth of 3 cm which is close to the maximum temperature elevation in the experiment. Fig. 3.15B illustrates that the steady state temperature elevation decreases with delay for experimental and simulated cases at a 3 cm depth.
Fig. 3.14  A) Experimental temperature elevation as a function of time at two different depths for a transducer of 1 MHz, $R=10$ cm, $D=10$ cm. Pulse=7 s (132 pulses), Delay=20 s.
B) Experimental and simulated temperature elevations at a depth of 2 cm with a 20 s delay.
Fig. 3.15  A) Experimental and simulated steady state temperature vs. depth in tissue.  \( f=1 \text{ MHz}, \ R=10 \text{ cm}, \ D=10 \text{ cm}, \ \text{Pulse}=7 \text{ s (132 pulses)}, \ \text{Delay}=20 \text{ s}. \)  
B) Experimental steady state temperature elevations vs. delay between pulses at the depth of 3 cm, \( f=1 \text{ MHz}, \ R=10 \text{ cm}, \ D=10 \text{ cm}, \ \text{Pulse}=7 \text{ s (132 pulses)}. \)
3.5 DISCUSSION

The dependence of the focal spacing on the transducer characteristics during high temperature ultrasound hyperthermia was established using computer simulations. This information is critical for the design of the transducers and the sonication parameters used in the clinical treatments. From these results, it is obvious that multiple sonications must be used to cover most of the clinically significant tumors.

Both the in vivo experiments and the simulations agree well that the multiple sonications can cause temperature build up in the tissues located between the surface and the target volume. If not controlled, this temperature elevation will cause unwanted tissue damage as was obtained earlier during ultrasound surgery [10]. From these results, it appears that several factors control the near-field heating. Increasing in the delay between the pulses as well as the frequency, or decreasing both the pulse duration and F-number appear to reduce the near-field heating. Only the pulse duration and delay between the pulses are controllable since the F-number and frequency are used to determine the focal size and thus, the spacing between the pulses. In addition nonlinear propagation [70] and cavitation threshold [68] set limits for both of these parameters.

For an F-number of 1 and transducer operating at a frequency between 1-1.5 MHz, the near-field heating can be reduced to acceptable levels by using a pulse length of 5 s or shorter and by having a delay of at least 20 s between the pulses.
These numbers are the worst case values, because of the small value for perfusion used in the model.

Both the spacing and the delay between the pulses have an impact on the treatment time. Consider a 1 cm x 1 cm x 3 cm tumor. If this tumor was to be treated using a 1 MHz transducer with an F-number of 1, a 1 s pulse, and a 20 s delay between pulses, then the 1 cm x 1 cm layer will be covered with 256 pulses (using a 0.625 mm radial spacing). The length of the tumor is 3 cm, which means that by using the axial spacing of 4.25 mm, the tumor must be partitioned into about 7 layers. Therefore the treatment time becomes 256 pulses/layer x 7 layers x 21 s/pulse or 10.45 hours. If the transducer F-number is changed to 2, the number of pulses is 64 (pulses/layer) x 2 (two layers total) = 128 pulses. The F-number of 2 though will increase heating in the near-field, thus the delay should be increased to 40 s. Then, the treatment time becomes 128 pulses x 41 s/pulse or 1.45 hours. Thus, a significant reduction in treatment time is achieved with high F-number transducers.

From these examples it is obvious that only small tumors such as in the eye or in the brain can be treated with a single spherically curved ultrasound transducer. Large tumors can be treated by creating larger focal zones without reducing the frequency or focusing (which are the only means to increase the focal size with spherically focussed transducers). There are several ways to do this: one can use lenses which either induce multiple foci or rings [71], [72], [73]. Second, multiple overlapping beams also allow larger focal size without loss in gain [74], [75]. Finally,
the focal size can be increased by using phased arrays. Such arrays have been
developed for standard hyperthermic purposes for example by Cain and Umemura [76]
and Ebbini and Cain [77].

As a conclusion, this study has established the requirement for focal spacing as
a function of transducer characteristics when spherically curved ultrasound transducers
are used to treat large target volumes. These treatments will require multiple
sonications which can cause temperature build-up outside of the focal zone. This
temperature elevation can easily reach levels which could cause tissue damage, and
thus increase the treatment volume outside of the target area. In spite of the fact that
all of the results presented in this paper are obtained for hyperthermic exposures of 60
equivalent minutes at 43 °C similar trends also apply for ultrasonic surgery [74], [78],
[79], [10].
CHAPTER 4

THE EFFECT OF VARIOUS PHYSICAL PARAMETERS ON THE SIZE AND SHAPE OF NECROSED TISSUE VOLUME DURING ULTRASONIC SURGERY.

4.1 Introduction.

Focused ultrasound can be used for non-invasive surgery during which the goal is to destroy preselected targets seated deep in the tissue, without any damage to the surrounding tissues.

The idea of high power ultrasound surgery was first proposed by Lynn et al. [6]. Since that time several experimental studies have been performed to investigate tissue necrosis induced by focussed ultrasound (for example [12], [19], [22], [28], [8], [9]). During the past few years ultrasonic surgery has received attention again due to the development of commercial devices which are now, or soon will, be under clinical testing [79], [42], [80], [81]. In addition, a system was developed that applies ultrasound in an MRI scanner [82], [10]. All of these developments have increased the potential applications of ultrasound surgery.

Predicting the threshold of necrosis received some earlier attention. For example [83], derived a model for predicting lesion size by using a threshold
temperature (found experimentally) for a given pulse duration. Various papers from the University of Illinois [22], [23], [26] proposed an acoustic intensity threshold for a given pulse duration in mammalian brain. Intensity thresholds were also proposed for the liver, kidney, and testicle of a rabbit [28], for bovine liver [8], and for the rabbit's eye [9]. However, the intensity or temperature threshold might not be the best quantity to define the formation of lesions. The development of lesion due to thermal damage can be defined best by thermal dose which links the temperature and time in a nonlinear fashion. The thermal dose concept was introduced to quantify the effectiveness of hyperthermia treatments during which the tissue temperature is not constant [7], [11].

The prediction of lesion size requires the knowledge of the thermal dose threshold that causes necrosis. Previous studies [84], [85], [86], [87], [88] have shown that the threshold thermal dosage reference at 43 °C is between 50 min and 240 min. The aim of this study was to predict the lesion size based on the evaluation of the 240 min thermal dose boundary, rather than on the intensity used or the resulting tissue temperature at the end of the ultrasonic pulse. This quantity allows us to execute a theoretical study to investigate the effect of various physical parameters on the size and shape of the lesions.
4.2 Model for numerical simulations.

4.2.1 Criterion for predicting tissue necrosis.

The criterion for predicting the tissue necrosis was based on locating the 240 min (at 43 °C) iso-dose line around the focus. Therefore, the lesion boundary is based on a threshold thermal dose value. The dose distribution was obtained by first calculating the power field using the methods of section 1.2.1. Then the temperature vs. time at each field point was calculated using the methods of section 1.3. Based on the temperature vs. time history the thermal dose distribution was calculated using the methods of section 1.4. The boundary of 240 min was selected because it appears to be close to the maximum experimental dose required for inducing tissue necrosis. The maximum temperature was limited to 100 °C, to avoid boiling which could distort the ultrasound field.

4.2.2 Calculation of the length and the diameter of the lesion.

Fig. 4.1A shows the acoustical power distribution for a 1 MHz transducer of 10 cm diameter and 10 cm radius of curvature. The focus was at approximately 10 cm, while the applied power was 40 W for 5 s. Based on this distribution, the temperature elevation was simulated as shown in Fig. 4.1B. The maximum
Fig. 4.1 A) Power density distribution for a 1 MHz transducer. Diameter = 10 cm, Radius of curvature = 10 cm, Power = 40 W, focus at the depth of 5 cm. B) Temperature elevation distribution of the power field in Fig. 1.A for a 5 s sonication and perfusion 0.5 kg/m³/s.
temperature elevation was seen at the focus and is about 50 °C. Based on the temperature distribution, the thermal dose distribution was then obtained as shown in Fig. 4.2A (the thermal dose values larger than $10^9$ min are not shown in the graph). The reader may note that the dose increases rapidly from one field point away from the focus, towards the focus. In Fig. 4.2B a contour plot with 120 min and 240 min iso-thermal dose curves is shown. The difference in the lesion diameter by using the values of 120 and 240 min is less than 0.1 mm, with the maximum difference located at the focus. The corresponding difference in the length is 0.4 mm with the maximum at the central axis.

4.2.3 Simulations of the in vivo experiments.

In the simulations of the experiments, the attenuation coefficient of 4.1 Np/m/MHz and the perfusion rate of 0.65 kg/m$^3$/s were used. These values were measured for thigh muscles of similar greyhound dogs in separate experiments [69].

4.3 Simulation results.

The focal intensity needed to cause necrosis was evaluated by finding the intensity that produced a thermal dose of 240 min at the focus. Fig 4.3A shows the focal intensity levels needed to cause necrosis as a function of frequency for a 5 s
Fig. 4.2 A) Thermal dose distribution referenced at 43 °C.
B) 120 min and 240 min iso-thermal dose contour line for the dose distribution in Fig. 4.2A.
Fig. 4.3. A) Intensity threshold for tissue necrosis vs. frequency for a 5 s pulse at the F-numbers of 1 and 2.
B) Intensity threshold for tissue necrosis vs. pulse duration for frequency of 1 MHz and F-number of 1 and 2.
pulse. The F-numbers of 1 and 2 were used. Fig. 4.3B shows the intensity threshold as a function of pulse duration for f=1 MHz (F-number 1 and 2) and a 5 cm depth in the tissue. Fig. 4.4A shows the threshold power vs. frequency for different F-numbers (1 and 2) for a 1 s pulse. Fig. 4.4B is the corresponding graph for 5 s. The lowest power is required at 2 MHz, since at that frequency the absorbed power density is maximized.

The effect of pulse duration on the lesion size is shown in Fig. 4.5. Fig. 4.5 shows 240 min isodose lines at a power of 20 W and a perfusion of 0.5 kg/m³/s for 5, 10, 30, and 50 s pulse durations. The lesion length and the diameter increased with increased pulse duration (Fig. 4.6A). The perfusion rate does not have an effect on the lesion dimensions for pulses of 10 s or shorter when the perfusion is between 0.5 and 10 kg/m³/s. At the perfusion rate of 100 kg/m³/s, the lesion size changes for every pulse duration. Fig 4.6B shows the same graph for a power of 50 W indicating that the lesion size is perfusion independent for pulse durations of 5 s or shorter at any of the perfusion rates studied. Most biological tissues have perfusion rates between 0.5 and 10 kg/m³/s, except for the kidney which has a perfusion rate of about 70 kg/m³/s [89].

Next, the effect of applied acoustical power on the lesion size was investigated. The contour plots as a function of acoustical power are shown in Fig. 4.7A and 4.7B for 1 and 5 s pulse durations, respectively. The lesion size increase as a function of applied power with the rate of increase dependent upon the pulse duration (Fig. 4.8).
Fig. 4.4 Threshold power vs. frequency for different F-numbers (1 and 2). A) for 1 s pulse duration B) 5 s pulse duration.
Fig 4.5 The 240 min iso-thermal dose contour lines for different pulse durations (Power=20 W).
Fig. 4.6 A) Lesion length and diameter vs. pulse duration for perfusion rates of 0.5, 10, and 100 kg/m³/s (Power=20 W). B) Lesion length and diameter vs. pulse duration for perfusion rates of 0.5, 10, and 100 kg/m³/s (Power=50 W).
Fig 4.7 The 240 min iso-thermal dose lines for different powers A) 1 s pulse, B) 5 s pulse.
Fig. 4.8 A) Lesion length vs. power induced by pulses of 1, 5, and 30 s long (Power=20 W).
B) Lesion diameter vs. power induced by pulses of 1, 5, and 30 s long (Power=20 W).
Finally, the effect of two transducer parameters was considered, the frequency and the F-number. Fig. 4.9A shows the change in the lesion length with frequency for a power of 50 W, a 5 s pulse duration, and an F-number of 1. Focal depths of 5, 10, and 15 cm were studied. Fig. 4.9B is the corresponding plot for the lesion diameter. Fig. 4.10A shows the change of lesion length with frequency at a constant intensity in the tissue (800 W/cm²) at depths of 5, 10, and 15 cm. Fig. 4.10B is the corresponding plot for the lesion diameter. The effect of F-number on the lesion length is shown in Fig. 4.11A at a depth of 5 cm (5 s pulse duration, 800 W/cm² and f=1 MHz). Fig. 4.11B is the corresponding graph for the diameter. Both length and diameter grow as a function of increasing F-number.

The lesion size was found to be only slightly dependent on the attenuation coefficient (Fig. 4.12). This behavior indicates that the results obtained in this study could be applied to most soft tissues. The maximum lesion size occurs when the attenuation is 10 Np/m/MHz. This can be proved mathematically by setting the derivative of dq/dα₀ (using equations 17-19) equal to zero. Then α₀max is given by

\[ \alpha_{0\text{max}} = \frac{1}{2\pi f} \]  

(49)
Fig. 4.9  A) Lesion length vs. frequency at different depths in tissue (5, 10, and 15 cm). Power=50 W (5 s pulse), Diameter=20 cm, Radius of curvature=20 cm. B) Lesion diameter vs. frequency for the case of Fig. 4.9A.
Fig. 4.10 A) Lesion length vs. frequency at different depths in tissue (5, 10, and 15 cm), Focal intensity = 800 W/cm² (5 s pulse), Diameter = 20 cm, Radius of curvature = 20 cm.

B) Lesion diameter vs. frequency for the case of Fig. 4.10A.
Fig. 4.11 Lesion length (A) and diameter (B) vs. F-number (5 s pulse, Intensity = 800 W/cm²).
Fig. 4.12 Lesion length (A) and diameter (B) vs. attenuation coefficient for a 5 s pulse (Power = 20 W).
For the simulations of Fig. 4.12 the frequency was 1 MHz and the focus was 5 cm deep, thus, from eq. 49 the maximum lesion size is obtained with 10 Np/m/MHz.

Fig. 4.13 shows the effect of applying multiple pulses on the ratio of length to diameter of the lesion for two different F-numbers (1 and 2).

![Graph showing the ratio of length to diameter vs. number of pulses for different F-numbers](image)

Fig. 4.13 Ratio of length to diameter vs. number of pulses at different F-numbers (1 and 2). f=1 MHz, pulse duration = 5 s, Delay between pulses = 5 s, Power = 30 W.
Increasing the number of pulses decreases the ratio (the decrease is faster for the F-number of 2). Thus, the sphericity of the lesion can be controlled up to a certain degree with adjusting the number of pulses.

Fig. 4.14 summarizes what happens in the axial thermal dose distribution when A) the pulse duration, B) the power, C) the F-number and D) the frequency are varied. The above graph helps the understanding of the lesion length development. Similarly, the lesion diameter development can be understood by considering the radial thermal dose distribution.

4.4 Experimental results

Fig. 4.15A shows experimental (dog's thigh) and simulated lesion diameter vs. pulse duration for a 1.688 MHz transducer and at a 64 W applied power level. The lesion diameter as a function of power for the rabbit experiment and simulations are plotted in Fig. 4.15B (5 s pulse duration and same transducer).

Fig. 4.16 shows the threshold intensity vs. pulse duration for brain (thermal dose threshold of 50 min at 43 °C was used). The value of this threshold was taken from [86]. Details of the experimental procedures can be found in [90]. At short pulses the experimental results do not agree with simulations because cavitational mechanisms dominate. Fig. 4.17A. shows the lesion length at different intensity levels in brain for different pulse durations. Fig. 4.17B. shows the corresponding
Fig. 4.14 Thermal dose distribution in the axial direction at A) Different pulse duration, B) Different power, C) Different F-number and D) Different frequency.
Fig. 4.15  A) Lesion diameter vs. pulse duration for experiments (dog's thigh) and simulations. Power=64 W, Frequency=1.688 MHz, Diameter=10 cm, Radius of curvature=10 cm, Focal depth=1 cm.  
B) Lesion diameter vs. power for experiments (rabbit's thigh) and simulations. Pulse duration=5 s. Frequency=1.688 MHz, Diameter=10 cm, Radius of curvature=10 cm, Focal depth=1 cm.
Fig. 4.16 Theoretical and experimental intensity threshold vs. pulse duration for brain. $f=0.936$ MHz, $R=7$ cm, $D=8.5$ cm, focal depth = 11 mm.
Fig. 4.17 Lesion size vs. intensity at different pulse durations in brain. 
A) Length and B) Diameter. $f=0.936$ MHz, $R=7$ cm, $D=8.5$ cm, 
Focal depth = 11 mm.
graph for the lesion diameter. It may be noted that, at low pulse durations, the mechanism is probably cavitation (the applied intensity is above the threshold of cavitation) and thus the experimental results show necrosis at lower intensities. Agreement is good for pulse durations of 0.5, 1, and 2 s. The agreement appears to be better for the diameter.

The accuracy of the model was also checked using results from the study of Basuri and Lele [16] on cat brain. In that study 464 cats were sonicated. The transducer diameter was 6 cm, the radius of curvature was 8 cm, and the frequency was 2.7 MHz. The attenuation coefficient of 2.4 Np/m/MHz was used, based on experimental data from [51]. Fig. 4.18A shows experimental and theoretical lesion length vs. pulse duration (6 W) in cat brain. Fig. 4.18B shows experimental and theoretical lesion length vs. power (pulse duration = 1 s). The trends of this graph are similar to those of Fig. 4.8, and Fig. 4.15B. Fig. 4.19 shows lesion length and diameter vs. number of pulses in brain (pulse duration = 0.4 s and delay between pulses = 1 s). In the simulations of Fig. 19, a temperature dependent attenuation coefficient was used based on data from [16]. The predicted lesions were much smaller when the temperature dependent attenuation was ignored. The effect of baseline temperature on the lesion size is demonstrated in table 4.1 for a 1.3 s pulse (10 W).
Fig. 4.18 A) Lesion length vs. pulse duration in brain (6 W), B) Lesion length vs. power in brain (1 s). $f=2.7$ MHz, $R=8$ cm, $D=6$ cm.
Fig. 4.19 Lesion length and diameter vs. number of pulses in brain (pulse duration=0.4 s, delay between pulses=1 s, power=10 W).
TABLE 4.1
EXPERIMENTAL AND THEORETICAL LESION LENGTH AND DIAMETER VS. BASELINE TEMPERATURE

\[ f=2.7 \text{ MHz}, R=8 \text{ cm}, D=6 \text{ cm}. \]

Pulse duration = 1.3 s, Power = 10 W.

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<tr>
<td>d (mm)</td>
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<td>0.74</td>
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</table>

Exp : experimental
Sim : simulated

4.5 Discussion

The experimental and the simulated results agree well indicating that the theoretical model can be used to give guidelines for the ultrasonic surgery. The small difference is attributed to uncertainties in measuring the lesion size and also in possible differences in the acoustical and thermal properties between experiments and simulations. The threshold intensity was also compared with experimental results found by other authors. Fig. 4.20 shows intensity thresholds for a given pulse duration. The data includes different organs (kidney, liver, brain, testicle, eye) and
Fig. 4.20 Threshold intensity vs. pulse duration measured in animal tissues by various authors.
different frequencies (1-9.8 MHz). The tissue type will affect the threshold as tissue type with higher attenuation have lower thresholds than tissue with lower attenuation. The main reason that intensity threshold in brain is lower than other tissues is that the thermal dose threshold for necrosis in brain is lower (50 min at 43 °C, [86]). The intensity thresholds of this study (of attenuation of 4.1 Np/m/MHz) agree well with those of [28], for the liver, kidney, and testicle (measured attenuation coefficients were 7, 4, 3 Np/m/MHz, respectively).

The theoretical threshold for short pulses (1 s or shorter) is higher than the experimental values obtained by other authors. A possible explanation for this is that the intensity applied is above the threshold value for transient cavitation which could increase energy absorption, and thus, reduce the required intensity for lesion formation [38], [68]. Transient cavitation may also cause direct mechanical damage of the tissue [78]. The results of the other authors, show only a small variation in the threshold with frequency [24]. This agree with the results with F-number 1 transducer which show only a small increase of intensity as a function of frequency. This can be explained by the fact that if a narrow beam transducer is used the thermal gradients and conduction effects are higher [24], requiring a higher intensity to achieve the same temperature and thermal dose.

The advantage of using the thermal dose to evaluate the lesion formation is that all parameters (sonication, transducer, and tissue properties) which influence lesion formation can be taken into account and experimental lesion thresholds (obtained by
any heating method) can be applied for estimating the lesion size and shape. This technique allows one to perform theoretical studies to optimize and evaluate sonication systems much more thoroughly than is feasible by using animal experiments at power levels where thermal effects are dominating. This correlation is not the case with the intensity threshold or temperature models which would not predict the lesion size well when transducer parameters are varied.

The lesion size can be controlled by adjusting the pulse duration and by adjusting the amount of acoustical power applied. The lesion size (length and diameter) increases with the pulse duration because the longer durations, produces higher temperature elevations and larger heated volumes due to thermal conduction. As a result, the boundary is pushed outward. However, during the longer sonications, the tissue temperature and thus, the lesion size, become dependent on perfusion rate. Most of the tissues (excluding kidney and liver) have perfusion values smaller than 10 kg/m$^3$/s [89]. For those tissues, the size is almost completely independent of perfusion for pulse durations of 10 s or shorter. For higher perfusion rates the independence of perfusion was lost at pulse durations greater than 5 s. The lesion size was found to be independent of pulse duration (longer than 20 s) for the high perfusion rate, since all the power absorbed is removed by perfusion. These results agree well with the simulation and experimental results of [65] who investigated the dependence of thermal dose on perfusion at hyperthermic dose levels.

An increase in power results in a higher temperature elevation and thermal
dose. Again the boundary is pushed outward. The rate of increase of the lesion size slows at higher values of power and longer pulse durations, because the thermal conduction effects responsible for the spreading of the temperature elevation have a limited range.

The size of the lesions can be changed by varying the focal shape and size which are controlled by the operating frequency and transducer geometry (F-number). The frequency has two effects on the thermal dose. The first effect is associated with the absorbed power density at the focus which is proportional to the absorption coefficient and the focal intensity. The absorption coefficient increases linearly with frequency and therefore the absorbed power density and the thermal dose increases with frequency. The attenuation coefficient increases with frequency and thus, less power reaches the focal depth at a higher frequency. This behavior will decrease the absorbed power density and the thermal dose. Thus, depending on the focal depth the thermal dose may increase or decrease as a function of frequency (increases close to skin since the drop of the intensity is small and decreases deeper in the tissue when attenuation effects dominate). In addition the frequency changes the shape of the power field (the focus gets narrower with increasing frequency). This characteristic will decrease the thermal dose at locations lying outside the power field. These effects that are sometimes competing will give maximum lesion size at a certain depth which is dependent on frequency (same acoustical power). As the focus is pushed deeper in the tissue, the range of frequency that causes necrosis at the focus is limited. By
applying the same intensity at the focus, the lesion size decreases with increased frequency monotonically since the narrowing of the field is the dominant effect.

The lesion length and diameter increases with increasing F-number because the focal size (axial and radial) of the acoustic field increases with the F-number (provided that the intensity is kept constant). The F-number is the major tool for increasing the lesion size. However, during treatments where multiple pulses are needed to cover a large volume, the temperature elevation in front of the focal zone sets a limit in the selection of the F-number [46].

The attenuation coefficient has two competing effects. A larger attenuation coefficient, means a higher absorption (increased thermal dose). However, the focal intensity decreases with increasing attenuation (decreased thermal dose). Because of this relationship the lesion size is not strongly dependent on attenuation coefficient and therefore, the simulation results can be applied for different soft tissues.

The theoretical and experimental comparison in the brain (using the data from [16] is very promising. The effect of baseline temperature in the lesion size was also demonstrated theoretically. The lower the baseline temperature the lower the lesion size (for a constant power) since the resultant tissue temperature and thermal dose are lower. The agreement between simulated and experimental lesion in brain at different pulse durations (6 W) is good for pulses 5 s or lower. The good agreement in this range was also reported in the study by Vidkotseva et al. 1993 [90]. The comparison of lesion length vs. power for 1 s pulse was good. Although the simulations predict
no lesion at the power of 6 W, the experiments showed lesion of 1.5 mm in length. At the highest power level (20 W), the agreement is not as good as in lower levels. The reason for that might be the fact that the absorption at high temperatures changes as a function of temperature [16], which is not accounted in that particular simulation.

The accuracy of the simulations is affected enormously by the degree of accuracy of the following parameters: a) the attenuation coefficient which is very critical for applications where the focus is few cms deep in the tissue, b) the value of the absorbed density in tissue which might be different from the predicted, and c) the iso-dose constant R (section 1.4) which varies form 0.4-0.8 from tissue to tissue [11]. The variability of the above parameters will affect the accuracy of the predicted lesion.
CHAPTER 5

SKIN DAMAGE DUE TO LESION PRODUCTION IN A HIGHLY-PERFUSED TISSUE SEATED A FEW CMS DEEP.

5.1 Introduction.

Since [6] published the first paper in ultrasonic surgery a lot of investigators studied different problems in the area of experimental ultrasonic surgery (for example [12], [19], [22], [28], [10]). However, emphasis was not given in developing theoretical models that can be used to predict different applications in the field of ultrasonic surgery. Only a few papers are noted in the literature, such as the papers by [8], [9].

One problem that was never studied before is the damage of the surrounding tissues produced when a highly-perfused tissue such as kidney or liver is sonicated with high intensity ultrasound. Skin damage was reported by Goss and Fry [91]. In that study sarcoma was implanted subdermally in hamsters. The tumor was treated with a 1.1 MHz transducer and an intensity of 907 W/cm² (7 sec). The transducer aperture diameter was 7.5 cm and the axial focal center was 13 cm. Skin damage during sonication of the kidney in a rabbit was also reported by [92].

In this study a theoretical approach is presented that optimizes sonication (pulse
duration and power) and transducer (frequency and F-number) parameters to avoid damage of the surrounding tissues to the kidney.

5.2 Model for numerical calculations.

5.2.1 Power field.

The ultrasound beam goes through four different layers (skin, muscle, fat and kidney). Thus, the power field was estimated using the model described by Fan and Hynynen 1992 (section 1.2.2). The thickness of each layer was calculated using MRI imaging. Fig. 5.1 shows the spherically focussed transducer in front of the four layers (not drawn to scale). Table 5.1 shows the thickness, attenuation coefficient, perfusion rate, and tissue density of each layer. In all simulations the focus was 15 mm deep in the tissue.

5.2.2 Temperature and thermal dose calculation.

The temperature was calculated using the perfusion rate specified in table 5.1. Based on the temperature history, the thermal dose was calculated using the formulation of section 1.4. To simplify calculations a unique thermal dose threshold for tissue necrosis was used for all four tissues (240 min at 43 °C).
Fig. 5.1 Transducer arrangement in front of the four layers.

TABLE 5.1

ACOUSTICAL AND THERMAL PROPERTIES OF EACH LAYER

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layer thickness</td>
<td>mm</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Attenuation coeff.</td>
<td>Np/m/MHz</td>
<td>14</td>
<td>4.1</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>Perfusion rate</td>
<td>kg/m³/s</td>
<td>0.5</td>
<td>0.65</td>
<td>0.93</td>
<td>70</td>
</tr>
<tr>
<td>Density</td>
<td>kg/m³</td>
<td>1200</td>
<td>1000</td>
<td>921</td>
<td>1040</td>
</tr>
</tbody>
</table>
5.3 Results

Fig. 5.2 shows absorbed power density distributions for three different F-numbers (0.8, 1.0, and 1.5), frequency of 1 MHz and power of 10 W. The focus in Fig. 5.2A lies entirely in the kidney. In Fig. 5.2B the focus lies 3 mm in the fat layer. In Fig. 5.3C the focus lies inside all four layers. The absorbed power density in the skin is high due to the high absorption of the skin. Fig. 5.3 shows the thermal dose in the left interface of a certain layer vs. pulse duration for the three different F-numbers. The dose in the focus (which lies in the kidney layer) was set to 240 min by adjusting the power. If the thermal dose in a layer is lower than 240 min, then no tissue damage is involved in the layer. When the dose is 240 min, then the onset of necrosis in the layer is reached. When the dose is higher than 240 min then necrosis in the layer of interest occurs. Fig. 5.3A shows the dose vs. pulse duration in the skin. No necrosis is seen at any F-number or any pulse duration. At the pulse duration of 1 s the dose is higher than the dose at 5 s. This is because the pulse duration of 1 s is short enough so that the conduction effect is small compared to the conduction effect at 5 s. In Fig. 5.3B the thermal dose vs. pulse duration is plotted for the muscle layer. For the F-number of 1.5 and pulse duration longer than 4 s necrosis is caused in this layer. The dose increases with pulse duration due to the increased conduction. The F-number of 1.5 causes necrosis at any pulse duration in the fat (Fig. 5.3C) since the length of the beam which lies in the fat has high
Fig. 5.2 Power density distribution in the axial direction for different F-numbers (0.8, 1.0, and 1.5). f=1 MHz, Power=10 W.
Fig. 5.3 Thermal dose of a certain layer vs. pulse duration at different F-numbers (0.8, 1.0, 1.5). A) Skin, B) Muscle, C) Fat.
values of power density. From the same graph (Fig. 5.3C) it appears that with F-number of 1 and pulse duration of 50 s necrosis will be caused in the fat layer. Table 5.2 shows the power needed to establish thermal dose of 240 min in the kidney at different pulse duration (1, 5, 10 and 30 s) and different F-number (0.8, 1.0, and 1.5).

| TABLE 5.2 |
| TABLE 5.2 POWER (W) NEEDED TO ESTABLISH 240 MIN IN THE KIDNEY AT DIFFERENT PULSE DURATIONS AND F-NUMBERS |

f=1 MHz, D=10 cm.

<table>
<thead>
<tr>
<th>F-number</th>
<th>Pulse duration (s)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>0.8</td>
<td>39.9</td>
<td>15.2</td>
<td>11.6</td>
<td>8.7</td>
</tr>
<tr>
<td>1.0</td>
<td>49.4</td>
<td>17.2</td>
<td>12.6</td>
<td>9.2</td>
</tr>
<tr>
<td>1.5</td>
<td>112.4</td>
<td>32.9</td>
<td>22.8</td>
<td>15.8</td>
</tr>
</tbody>
</table>
Since the transducer with the F-number of 0.8 does not cause any damage in the surrounding tissues at any pulse duration, it is the best choice for producing lesions in a highly-perfused organ seated a few cms deep. Using this F-number, the power needed to cause necrosis in the surrounding layers was studied as a function of pulse duration and frequency (Fig. 5.4). The threshold power increased with decreasing the frequency and the pulse duration.

Fig. 5.5 shows the thermal iso-dose lines for a transducer with an F-number of 1. The frequency used is 1 MHz and the power is 20 W (at pulse duration of 5, 10, and 30 s). It can be noted that with pulse durations of 5 and 10 s the necrosed volume lays entirely in the kidney (skin starts at 8.5 cm and the kidney at 9.2 cm in the axial direction). For pulse duration of 30 s, the dose in the fat and part of the muscle exceeds the critical dose (240 min) and thus undesired necrosis is caused. Using higher F-number (1.5) causes prolonged necrosis in the axial direction due to the long axial beam (Fig. 5.6). At the pulse duration of 10 s the lesion lays in the fat instead of the kidney, because the fat layer has higher absorbed power density than any other layer. Localized lesions in the kidney are best produced using an F-number of 0.8 (Fig. 5.7). The lesions are of ellipsoidal shape, similar to the lesions shown in chapter 4. The rate of increase of the lesion size with time drops eventually.
Fig. 5.4. Power needed to cause necrosis in the surrounding layer as a function of pulse duration and frequency (F-number=0.8).
Fig. 5.5 Iso-dose line (240 min) at different pulse durations for $f=1$ MHz, $R=10$ cm, $D=10$ cm, Power=20 W.
Fig. 5.6 Iso-dose line (240 min) at different pulse durations for $f=1$ MHz, $R=15$ cm, $D=10$ cm, Power = 20 W.
Fig. 5.7 Iso-dose line (240 min) at different pulse durations for f=1 MHz, R=8 cm, D=10 cm, Power=20 W.
5.4 Discussion.

The heating of the skin can be avoided by properly selecting the pulse duration, the power, the F-number, and the frequency. The main parameter to eliminate the heating of the skin is the F-number. An F-number of 0.8 or smaller is the best choice because the focal size is small enough and, thus, the necrosis is confined to the kidney. For pulse durations smaller than 30 s and F-number of 0.8 no necrosis is caused in any surrounding layer when the power that establishes necrosis in the kidney is applied. If longer pulse durations are applied, then necrosis will be caused in the surrounding layers (starting with the fat and then muscle, and skin).

Increasing the frequency increases the absorption, and thus the power to cause necrosis in the surrounding layers decreases. At the frequency of 1.5 MHz the threshold power to cause necrosis in the surrounding tissues is almost independent of the pulse duration for pulse durations longer than 5 s. With 5 s pulse duration that threshold power is only 20 W. Thus, the power range for lesion production for this frequency is limited. The power threshold to cause necrosis in the surrounding layers for the frequency of 0.5, and 1 MHz is much higher and it is above the threshold of cavitation. This power threshold drops with increasing pulse duration. Since the 1 MHz case has higher cavitation threshold, this frequency is preferred.

This study can be applied to other applications where highly perfused tissues are to be sonicated (for example liver). The same problem will exist when humans
are to be treated. However, in that case the kidney will be a few cms deeper, and thus, the beam will be attenuated more. Thus, higher power, longer pulse duration, slightly higher frequency, and slightly higher F-number can be used.

Although short pulses are advantageous due to the insensitivity to blood perfusion, when sonicating highly-perfused tissues longer pulse durations may be used. This is needed so that lesions of adequate size can be created, since the heat removed by the high blood perfusion is more important for this application. Unfortunately, perfusion variations during treatments might affect the lesion size. However, if imaging of the lesion (such as MRI) is available, then the power can be adjusted to establish the desired lesion size. Thus, using long pulses, larger lesion volumes can be achieved and thus, the treatment time will be reduced.
CHAPTER 6

MRI IMAGING IN CONJUNCTION WITH ULTRASOUND THERAPY.

6.1 Introduction to MRI (summary from [93]).

The core of the atom that accommodates most of the elemental mass is called the nucleus; it consist of protons and neutrons. Certain nuclear species possess angular momentum or spin, and thus some nuclei can be thought of as behaving like small spinning spheres. Since nuclei bear electric charges, their spinning produces a magnetic moment \( \mu \), expressing the strength and the direction of the magnetic field surrounding the nucleus. When exposed to static magnetic field, the randomly oriented magnetic dipoles line up with the magnetic field. For the proton (the principal isotope of hydrogen), there are two allowable states corresponding to magnetic quantum numbers \( m = \pm 1/2 \) pertaining to low and high energy states. The spin vectors experience a torque when subjected to a magnetic field. As a result, they precess around the axis of the magnetic field at a rate given by the Larmor relationship

\[
f = \gamma B_0,
\]

(50)
where $f$ is the resonance frequency, $\gamma$ is the gyromagnetic ratio which is characteristic of every isotope, and $B_0$ is the static magnetic field. A net magnetic moment can be defined due to the random phases of the magnetic moments. This net magnetic moment is responsible for the induction of the magnetic resonance (MR) signal in the receiver coil.

Resonance is the induction of transitions between two different energy states. The energy required to produce a transition is the difference in magnetic energy between the lower and the upper energy states. Resonance occurs when radio frequency (RF) energy is applied at the Larmor frequency, flipping the magnetic moments from the lower state to the high energy states. Magnetic resonance absorption can be detected only if transverse magnetization (perpendicular to $B_0$) is established. According to Faraday's Law, this will induce a voltage in a properly oriented receiver coil. Transverse magnetization is created when a small RF field of amplitude $B_1$ rotating synchronously with the precessing spins is applied. Similar to the magnetic moments sensing the force of the static magnetism, the same happens with the net magnetic moment sensing the RF field. If the duration of $B_1$ is long enough the magnetization might rotate up to 90 degrees. The angle of rotation $\theta$ (RF flip angle) is given in terms of the duration $\tau$ of $B_1$ by

$$\theta = \gamma B_1 \tau,$$

(51)
T₁ relaxation

RF excitation causes the nuclei to absorb energy lifting them to the excited state. When the energy is dissipated the nuclei return to the ground state. This process is called spin lattice relaxation. T₁ is the time needed for the signal to reach 63% of its full value. Lattice fields produced from neighboring magnetic nuclei are responsible for relaxation. Small molecules like water reorient more rapidly than larger molecules. In mammalian tissues T₁ is in the order of hundreds of ms.

T₂ relaxation

Nuclei in the excited and the ground state exchange energy with each other (i.e. while one nucleus absorbs energy, its neighbor releases energy). The transverse magnetization decays because the magnetic moments get out of phase due to mutual interaction. Magnetic field imperfections lead to inhomogeneities which causes the nuclei to process at slightly lower rates. The difference in resonance of the nuclei results in phase coherence and, thus, a loss of transverse magnetization takes place. Therefore, the signal in the receiver drops with time. The time needed for the transverse magnetization to drop to 37% of its initial value defines the T₂ relaxation time constant. Typically, T₂ in biological tissues varies from 50 to 100 ms. The T₂ value of lesions is prolonged compared to normal tissue and this will result to good contrast between normal and necrotic tissue.
Spin echo

Due to spatial inhomogeneity of the magnetic field, the transverse magnetization decays much faster with a time constant $T_2^*$. Spins at different locations experience slightly different magnetic fields, thus causing different precession frequencies. As a result, the transverse magnetization shrinks faster than it would on the basis of $T_2$ processes alone. A 180 degree pulse applied for time $\tau$, establishes phase coherence $2\tau$ ms after a 90 degree pulse was applied. The period between the initial 90 degree pulse and the echo is denoted echo delay (TE).

Principle of imaging

When the magnetic field is varied linearly along a certain axis, the resonance frequency becomes dependent on the location of the volume element of interest. Signals are collected from different locations and the free induction decay (FAD) consists of many different frequencies (FAD is the case where the field is removed and hence the magnetization is subjected to the effect of the static magnetic field only). In the absence of the gradient, all locations would resonate with the same frequency and all locations would be indistinguishable. With the application of a gradient, however nuclei will resonate at different frequencies according to their position. To determine individual frequencies, a mathematical analysis called the
Fourier transform is performed. The FAD represents the time evolution of the transverse magnetization; the Fourier transform is its frequency analog. This correspondence allows extraction of the individual frequencies as well as their associated amplitudes which are proportional to the spin density at a certain spatial location.

**Pixels and Voxels**

Each plane is partitioned into a grid of rectangular picture elements (pixels). The intensity of each pixel represents the strength of the MR signals emitted from the region contained within the pixel. A voxel or volume element is a 3D extension of a pixel, the third dimension being the slice thickness. The typical values for a slice is from 1 to 10 mm thick. The term voxel is used for a 3D images volume elements.

**Image size**

The size of an MR image refers to the number of pixels. The most common MR images are a grid of 256 columns and 256 rows of pixels. The total number of pixels is $256 \times 256 = 65,556$. Images with more pixels have higher resolution. Some techniques for MR angiography and spine images produce images with 512 columns by 512 rows.
Image Intensity

No standard scale exists for the intensity of MR images. Most often the intensity is proportional to the amplitude of the magnetization vector or MR signals emitted by structures within the voxel. The term proton density image, T₁ image and T₂ image are often used. These terms refer to the relative weight with which the three parameters affect the contrast in MR images. The absence of a standard scale for MR image intensity makes it difficult to compare images. It is meaningless to compare the intensity of muscle, for example to be 500 in one image with another image, that has a value of 300. The two images might come from the same animal or patient, same machine and the same imaging technique, but the intensities are completely different due to different settings of the gain of the receiver. Images can be compared if their intensity is normalized relative to the same feature. The standard deviation of a certain location provides useful information on the background noise.

Signal to noise ratio (SNR)

The SNR expresses the strength of the signal relative to the noise which distorts an MR image. Alone neither the signal nor the noise is an informative measure of image quality. However, the SNR is the most significant measure of image quality. The signal is the mean intensity within a region of interest (ROI) over
a certain area of tissue. The noise is the standard deviation within an ROI in the background containing only noise. The noise in MR images originates from three sources: a) patient, b) electric resistance of receiver coil and c) electric interactions between receiver coil and patient. Patient noise arises from RF emissions associated with the random Brownian motion of molecules.

**Echo time (TE)**

The time from the center of the RF excitation to the center of the echo is the echo time. The signals decay with time because of $T_2$ relaxation times and other processes that dephase the transverse magnetization. The amplitude of the transverse magnetization depends on $T_2$ and the $T_2$ of the tissue ($e^{-\frac{TE}{T_2}}$). When $TE=T_2$ the magnetization decays to 37%. Adjusting $TE$ influences the contrast between tissues that have different $T_2$ times, since the shorter the $T_2$, the faster the decay; increasing $TE$ creates more contrast between tissues with different $T_2$ times.

**Repetition time (TR)**

The repetition time is the interval between consecutive repetitions of a pulse sequence. The value chosen for TR influences the amount of $T_1$ relaxation between RF pulses. $T_1$ relaxation allows the longitudinal magnetization to recover after an RF
pulse. The fraction that recovers is $1-e^{-\frac{TR}{T_1}}$ (assuming TE is much smaller than TR).

If TR=$T_1$ the longitudinal magnetization recovers to 63% of its maximum value.

The TR affects the contrast between the tissues that have different $T_1$ times. The longitudinal magnetization of longer $T_1$ tissues recovers slowly. Shortening TR creates more contrast between tissues with different $T_1$ times.

**Slice orientation**

The orientation of the slice depends on which of the three magnetic field gradients are activated during the RF pulse. By convention, the z gradient is directed along the bore of the magnet. The horizontal and the vertical gradients are usually denoted the x and the y gradients, respectively. If an animal is positioned head first and supine, an RF pulse in the presence of a z gradient creates a transverse slice. The x and y gradients select slices in the sagittal and coronal orientation, respectively. Oblique slices are created by activating two or more gradients during an RF pulse. The angle of the oblique slice depends on the relative strength of the x and the y gradient. If both gradient pulses have the same amplitude the slice angle is 45 degrees. The advantage of oblique slices is that their orientation might conform more closely to a specific anatomic structure. Slice interference occurs when multiple slices are imaged concurrently (due to slice interrupt $T_1$ relaxation in the region of overlap). This interruption occurs twice because slices on both sides are imaged.
RF thickness

A typical RF pulse has a bandwidth of 1 kHz. A narrower bandwidth affects the magnetization within a narrower strip of Larmor frequencies. Narrower bandwidth pulses produce thinner slices. Generally, slice thickness depends on both the amplitude of the slice-selection gradient pulse and the bandwidth of the RF pulse. The amplitude of the slice gradient pulse is used to adjust the slice thickness. Suppose that a 5 mm slice is desired with a bandwidth of 1 kHz. The amplitude of the gradient is 4.7 mT/m. A 2.5 mm slice thickness is achieved by doubling the gradient (9.4 mT/m). Thin slices are desired because they provide higher spatial resolution. The maximum gradient of the machine provided imposes a limit on the slice thickness. If the magnetic field is 1.5 T, the frequency of the RF pulse is about 63.87 MHz. The gradient makes the Larmor frequency proportional to position. Thus, the position of the slice depends on the frequency of the RF pulse and the magnitude of the gradient. For example if the gradient is 5 mT/m and the slice is 100 mm from the center then, the frequency of the RF pulse is (5 mT/m x 1 m x 42.52 MHz/T x 1.5 T=21 kHz from the center. Thus, the slice position is controlled by the frequency of the RF pulse for a fixed gradient.
Field of view (FOV)

The FOV is the distance between the edges of an MR image. The boundaries of the FOV occur where the MR signals have the highest frequency that can be sampled. The FOV influences the size of the pixels, which in turn controls the spatial resolution. Reducing the FOV or increasing the number of pixels provides higher spatial resolution.

Averaging (NEX)

Normally, repeating a sequence exactly should generate the same MR signal. However, due to noise the measurements differ. Since, the noise is random there is no correlation between the two images. Averaging two or more sets of data measurements has no effect on MR signals. However, averaging reduces the noise measured with the signals. Averaging improves the SNR by lowering the noise. The number of repetitive sets is denoted NEX (number of excitations). Averaging increases the SNR in proportion to $(NEX)^{1/2}$. Increasing the NEX from 1 to 4, will increase the SNR from 1 to 2. The disadvantage of increasing the NEX is the data acquisition time increase.
Acquisition time

The acquisition time depends on the repetition time (TR), the averaging (NEX) and the number of matrix points in the plane where the gradient is applied (N). Decreasing any of the above numbers will decrease the acquisition time. A sequence with TR=500 ms, N=128, and NEX=2 is acquired in \( 128 \times 0.5 \times 2 \) s = 128 s or 2.1 min. If 10 slices are needed, then the image time is \( 10 \times 21 \) = 21 min. Shortening TR will reduce the image time, but this will affect the contrast. Reducing NEX might have a critical effect on the SNR. Only if the intrinsic noise is low can the minimum NEX of 1 be used. Reducing N will affect the spatial resolution. Thus, depending on which parameter is important (contrast, SNR, spatial resolution) either TR, NEX, N can be varied accordingly.

Rapid scan techniques

It is very important in short pulse ultrasound to acquire the data quickly so that the temperature change is monitored. Also, during clinical treatments in the future this quicker acquisition time this will minimize treatment time.

One technique which belongs to the class of gradient-echo pulse sequence (well documented in many MRI books) is the GRASS (gradient recalled acquisition in steady state). Provided that TR is long (several hundreds of ms) the steady state
effects are negligible and the signal obeys the following relationship

$$S = N(H) \frac{(1-e^{-\frac{TR}{T_1}})}{1-\cos\theta e^{-\frac{TE}{T_1}}} \sin\theta e^{-\frac{TE}{T_2}},$$  \hspace{1cm} (52)$$

where $N(H)$ is the proton density. If $TE < T_2$ and $\theta = 90^\circ$ the equation becomes

$$S = N(H)(1-e^{-\frac{TR}{T_1}}).$$  \hspace{1cm} (53)$$

Under these conditions the image is said to be $T_1$ weighted. If $\theta < 90^\circ$, then $S = N(H)$. Under this last condition the image is said to be proton density weighted. If $TE$ is long, then $S = e^{-\frac{TE}{T_2}}$ and the image is said to be $T_2$ weighted.

Different contrast is achieved if the residual magnetization is destroyed by spoiling. Spoiling can be achieved using spoiling gradients or by using radio-frequency spoiling. This sequence is called spoiled GRASS (SPGRASS). The acquisition time of this sequence is the same with the acquisition time of GRASS if the same parameters are used.
6.2 Sonication system used inside the MRI scanner.

6.2.1 Description of system.

In order to avoid distortion of the images, the ultrasound system was designed with a minimum amount of magnetic materials. The system consists of a sonication system with the same equipment as the system described in chapter 2. Fig. 6.1 shows the block diagram of the sonication system used inside the MRI scanner. The transducer is moved in the X, Y and Z directions using a hydraulic system. The movement for each axis is established by two cylinders and a tube interconnecting the two cylinders. One cylinder is interfaced with a stepper motor (master) and the other cylinder is interfaced with the transducer (slave). Any movement in the master cylinder is followed by the slave cylinder and movement of the transducer is achieved. Each cylinder is filled with degassed water. The length of the water-filled cylinder is about 12.5 cm, which determines the range of each axis. The cylinders are connected with 50 feet of superthane ether tube filled with degassed water. The length of the tube is long enough to place the system outside the MRI room. The transducer with the cylinders and the mechanical interface are immersed in a box 84 cm long, 34 cm wide, and 14.2 cm high. The box is filled with degassed water and covered with a PVC membrane. An O’ring is used to seal the membrane onto the box. The stepper motors are controlled by a PC using an RS 232 serial port. The stepper motors
Fig. 6.1 Sonication system used inside the MRI scanner.
drivers are made from Oregon Micro Systems Inc. The motors provide controlled acceleration to a predefined peak speed followed by a constant velocity and controlled deceleration to a stop. Each axis can be moved independently or synchronized with other axes. The software controlling the movement of the transducer and the sonication was written in Quick Basic. Limit switches are used to prevent the positioner from hitting the walls of the box (manufactured by GE medical Systems).

6.2.2 Calibration

The first step in the calibration is to determine the distance moved due to the application of a certain number of steps. This process is shown in Fig. 6.2A. Using linear regression, the equation relating the number of steps and the distance moved was found. This equation is useful since the steps required to move the positioner a certain distance can be estimated. It seems that the positioner begins to move when 664 steps are applied. Using the equation found from Fig. 6.2A, steps were applied to move the positioner 1, 5, 10, and 20 mm (40 movements for each case). The resultant distance moved vs. intended distance is shown in Fig. 6.2B. Fig 6.2C shows the maximum error increasing with the distance moved. But Fig. 6.2D shows that the average error does not necessarily increase with distance moved. Fig. 6.3 shows histograms for distances of 1, 5, 10 and 20 mm. The range of the graphs is in steps of 0.05 mm. The peak occurs close to the intended distance moved (within 0.05 mm).
Fig. 6.2 A) Graph of steps vs. distance moved.
B) Resultant distance vs. intended distance for 1, 5, 10 and 20 mm.
C) Maximum error vs. distance moved.
D) Average error vs. distance moved.
Fig 6.3 Histogram for 1, 5, 10, and 20 mm.
Fig. 6.4 Scatter plot for 10 mm movements.
Fig. 6.4 shows a scatter plot of distance moved vs. measurement step (for 10 mm movement). The importance of this plot is that there is no decrease in distance moved with measurement number, indicating that there were no leaks in the system. The movement of long steps (80 mm) was tested also. It was found that the maximum error was 0.4 mm and the average error was 0.051 mm.

6.3 Effect of transducer on the quality of the image.

The objective of these experiments was to investigate how the transducer and its interconnection to the sonication system affect the imaging. The procedures of this section can be applied for any ultrasonic system that is going to be placed inside an MRI scanner. The required hardware used is simple and inexpensive.

A phantom representing bone and tissue was designed. Nylon was selected as the material to represent bone since it has similar optical properties with the bone. Three square plates (10x10 cm²) of 6 mm thickness were prepared. The plates were spaced by 2 cm. Holes were placed in each plate to study the effect of transducer in measuring distances. In two plates 12 identical holes were opened. Fig. 6.5 shows the image of one of the plates with this pattern. In the third plate holes of different diameter (1, 2, 3, and 4 mm) were opened (Fig. 6.6). The pattern of the holes was duplicated twice. This plate was designed in order to study the effectiveness of imaging small dimensions and to study whether the transducer had any effect on
Fig. 6.5 Image of 1st plate with the 12 holes representing the bone.

Fig. 6.6 Image of 2nd plate that is used to study the resolution and effect of transducer on the resolution.
measuring small dimensions. The bone phantom was immersed in a bath of saline which represents the tissue. A coil was placed in the bottom of the bath to improve the signal reception.

6.3.1 Imaging

Two different imaging techniques were used. In both techniques, the following parameters were used: TR=4000 ms, TE=18 ms, slice thickness=4 mm. In the first technique, the matrix was 512x512 and NEX=4. Since the number of rows and columns was large, this technique provided high resolution. The other technique had a 256x256 matrix and NEX=8. This technique had smaller resolution, but better signal to noise ratio. In both imaging techniques, the acquisition time was 8.32 min.

6.3.2 Results-discussion.

Two different types of transducers were used. The first type was a 10 cm spherically focussed single transducer and the second type was an array of six transducers. Each transducer in the array was a 5 cm spherically focussed transducer. Fig 6.7 shows the image of the bone phantom immersed in saline. Fig 6.8 shows the image of the single transducer under the bone phantom (both immersed in the saline bath). Fig. 6.9 shows the image of the array of transducers under the bone phantom.
Fig. 6.7 Image of the plates representing bone immersed in sealing bath.

Fig. 6.8 Image of phantom and a single spherically curved transducer.
Fig. 6.9 Image of phantom and array of six transducers (only two shown from this angle).

Note that the presence of the transducers does not affect the image quality. A small distortion on the image is seen near the surface of the transducer.

The presence of the transducer (single or array) in the phantom did not affect the image quality or the effectiveness of the MRI system in measuring distances. The only noticeable effect was a drop in the signal intensity (about 10 %) when the transducers were present. The drop of intensity was spatially uniform (< 5 %) and thus, if the intensity was to be used for monitoring temperature changes, this drop would not be affected. The drop of intensity was more noticeable close to the transducer surface while at a distance of about 3 cm from the transducer, the intensity was not affected. Since the temperature changes occur mostly on the focus (the focus
is 10 cm deep for this transducer), the drop of intensity within 3 cm from the surface of the transducer has essentially no effect.

The effect of transducers in measuring distances was minimal. Both imaging techniques showed that the change in measuring a certain distance was in the order of the machine's resolution. Table 6.1 shows the diameter of six of the twelve holes calculated using the high resolution technique (without any transducer) and the diameter calculated with the same technique (with the transducer).

TABLE 6.1
MEASURED DIAMETER OF HOLES WITH TRANSDUCER AND WITHOUT TRANSDUCER (USING THE HIGH RESOLUTION SEQUENCE).

<table>
<thead>
<tr>
<th>Diameter without transducer (mm)</th>
<th>Diameter with transducer (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.54</td>
<td>4.53</td>
</tr>
<tr>
<td>4.68</td>
<td>4.69</td>
</tr>
<tr>
<td>4.79</td>
<td>4.77</td>
</tr>
<tr>
<td>4.54</td>
<td>4.55</td>
</tr>
<tr>
<td>4.71</td>
<td>4.70</td>
</tr>
<tr>
<td>4.59</td>
<td>4.60</td>
</tr>
</tbody>
</table>
6.4 Signal intensity vs. temperature of biological tissue in vitro.

6.4.1 Introduction

The possibility of using MR imaging in hyperthermia was studied by [94], [95], and [96]. Several authors demonstrated the use of MR imaging in monitoring interaction of tissue and heat. Jolesz et al. [97] reported monitoring of tissue damage during laser energy deposition. The main conclusion from that study was that signal intensity changes due to temperature were not followed immediately by MR due to hysterisis between signal intensity and temperature. Castro et al. [98] and Anzai et al. [99] imaged tissue damage during interstitial laser phototherapy. The volume of histological damage was observed by applying different energies. Mutsumoto et al. [100] monitored laser and freezing induced ablation in liver using MR imaging. The possibility of monitoring ultrasound surgery was first reported by [101], [82], and [10]. In these studies, a system was designed that applies ultrasound inside the MR tube, while at the same time monitoring the ultrasound-tissue interactions is obtained using MRI (section 6.2).

The aim of this study, is to examine the possibility of monitoring changes in temperature by estimating changes in signal intensity. The study was done in excised dog and rabbit tissue (muscle, kidney, liver, fat, and bone). The GRASS (Gradient-recalled acquisition in the steady state) and SPGRASS (Spoiled GRASS) imaging
techniques were used, since previous studies [102] showed that good sensitivity of signal intensity with temperature was achieved (experiments in vivo).

6.4.2 Sample Preparation and heating.

Muscle, kidney, liver, fat and bone were excised from greyhound dogs and rabbits. Four dogs and three rabbits were used totally. The tissues were placed in a solution of saline.

The samples were immersed in a plastic box. The box was filled with saline to preserve the samples. A 50 ft (15 m) long tube was used to connect the box with a heat exchange device. The heat exchange device was immersed in a heated water bath (MT Lauda, Germany). The maximum temperature of the bath was 100°C. A pump was used to circulate the water throughout the system. A thermocouple made of constantan and manganin was immersed in the bath and connected with a long wire set to a temperature reader (Baily instruments, Model TH-8, Saddle Brook, NJ) with a resolution of 0.1 °C. The thermocouple was calibrated using a mercury thermometer.

6.4.3 MRI Imaging

The imaging was done by using a 1.5 T scanner (Signa, Made by GE Medical Systems, Milwaukee). The GRASS and SPGRASS sequences were used in all the
experiments.

The echo time (TE) was 16 ms and slice thickness was 5 mm. The signal intensity was measured by selecting a region of interest with small area (0.04-0.08 cm²) since small areas provided good signal to noise ratio. The intensity of 4 different locations was averaged to reduce the effect of noise.

6.4.4 Results.

Fig 6.10 shows the plot of normalized signal intensity vs. temperature for each tissue type (except fat) for one of the dogs at three different repetition times (100, 50, and 20 ms). The intensity drops with temperature for all three repetition times. The intensity stays approximately constant when the tissue is denaturated by the heating. The disadvantage of using short repetition time such as 20 ms, is that the absolute signal intensity is low and comparable to the noise level. Fig. 6.11 shows the normalized signal intensity vs. temperature for each repetition time with all tissue type (dog) included in one graph. The reader may note that the signal intensity in bone and fat continued decreasing, even at the last temperature point. Fig. 6.12 shows normalized signal intensity vs. temperature (for dog muscle) for each repetition time for both GRASS and SPGRASS sequences. Fig. 6.13, 6.14, 6.15, and 6.16 are the corresponding graphs for kidney, bone, fat, and liver for the dog.

The variability from experiment to experiment (in dog) is shown in Fig. 6.17
Fig. 6.10 Normalized signal intensity vs. temperature for each tissue (dog) at different repetition times (GRASS imaging).
Fig. 6.11  Normalized signal intensity vs. temperature for each repetition time with all tissue types (dog) plotted in the same graph (GRASS imaging).
Fig. 6.12 Normalized signal intensity vs. temperature for dog muscle at different repetition times comparing GRASS and SPGRASS.
Fig. 6.13 Normalized signal intensity vs. temperature for dog kidney at different repetition times comparing GRASS and SPGRASS.
Fig. 6.14 Normalized signal intensity vs. temperature for dog bone at different repetition times comparing GRASS and SPGRASS.
Fig. 6.15 Normalized signal intensity vs. temperature for dog fat at different repetition times comparing GRASS and SPGRASS.
Fig. 6.16 Normalized signal intensity vs. temperature for dog liver at different repetition times comparing GRASS and SPGRASS.
Fig. 6.17 Normalized signal intensity vs. temperature A) in dog muscle and B) in dog liver showing the variability with experiments (GRASS imaging, TR=100 ms).
where the normalized signal intensity vs. temperature is plotted for dog muscle and liver for three different experiments. The same sequence parameters were used (TR=100 ms, TE=5 ms, slice thickness=5 mm). Note that the repeatability of results is very good in the range of 30-43 °C. At this range the tissue samples were heated fast, and no denaturation was observed. Heating the samples in the upper temperature ranges required longer time (due to heat loss by conduction) and the samples were denatured eventually. It was observed that the signal intensity was not repeatable at that range. Thus, the signal sensitivity with temperature is best evaluated in the lower temperature range (30-43 °C). Table 6.2 shows the slope (%/°C) for the 5 tissue types (dog) from the range of 30-55 °C. The slope was calculated using linear regression analysis. A minimum, maximum and average value is derived based on all the experiments performed. Table 6.3 shows the corresponding table for the range of 30-43 °C.

Fig. 6.18 shows the normalized signal intensity vs. temperature in rabbit tissues. The signal intensity was normalized using the intensity of 37 °C since in treatment the animal's or human's temperature is 37 °C. The slope of normalized intensity and temperature is different for a different starting temperature. The difference in the slope if 32 °C instead of 37 °C is used, is around 4%. Fig. 6.19 shows the normalized signal intensity vs. temperature for rabbit muscle for the three different experiments (different rabbit). Table 6.4 shows signal sensitivity with temperature in rabbit tissues with starting temperature of 37 °C.
TABLE 6.2
SIGNAL INTENSITY SENSITIVITY (%/°C) FOR DIFFERENT TISSUE TYPE (4 DOG EXPERIMENTS) EVALUATED IN THE RANGE OF 30-55 °C.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Signal intensity sensitivity (%/°C)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
<td>Highest</td>
<td>Average</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.5</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.6</td>
<td>2.2</td>
<td>1.86</td>
</tr>
<tr>
<td>Liver</td>
<td>1.25</td>
<td>1.63</td>
<td>1.44</td>
</tr>
<tr>
<td>Fat</td>
<td>1.6</td>
<td>1.85</td>
<td>1.72</td>
</tr>
<tr>
<td>Bone</td>
<td>1.3</td>
<td>2.24</td>
<td>1.85</td>
</tr>
</tbody>
</table>
TABLE 6.3

SIGNAL INTENSITY SENSITIVITY (%/°C) FOR DIFFERENT TISSUE TYPE (4 DOG EXPERIMENTS) EVALUATED IN THE RANGE OF 30-43 °C.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Signal intensity sensitivity (%/°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.6</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.6</td>
</tr>
<tr>
<td>Liver</td>
<td>1.2</td>
</tr>
<tr>
<td>Fat</td>
<td>1.3</td>
</tr>
<tr>
<td>Bone</td>
<td>1.53</td>
</tr>
</tbody>
</table>
Fig. 6.18 Normalized signal intensity vs. temperature in rabbit muscle for different tissue types (GRASS imaging, TR=100 ms).
Fig. 6.19 Normalized signal intensity vs. temperature in rabbit muscle showing the variability with experiments (GRASS imaging, TR = 100 ms).
<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Signal intensity sensitivity (%/°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.40</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.07</td>
</tr>
<tr>
<td>Liver</td>
<td>1.12</td>
</tr>
<tr>
<td>Fat</td>
<td>1.47</td>
</tr>
<tr>
<td>Bone</td>
<td>1.18</td>
</tr>
</tbody>
</table>
6.4.5 Discussion

Both GRASS and SPGRASS detect the change of signal intensity with temperature. The difference in signal intensity for the two sequences was less than 10% except for the case in fat (TR=50 ms) and kidney (TR=100 ms) of a dog. All repetition times that were used (100, 50, and 20 ms) gave very close qualitative and quantitative results. The repetition time of 100 ms has the advantage that the absolute intensity levels are much higher than the noise level. However, if fast imaging is required (during clinical treatments) then, the repetition time of 20 ms could be a better option.

The signal sensitivity of dog tissues evaluated using the whole range of temperature (maximum temperature defined as the point where the signal stays constant) has a wide range from experiment to experiment for a certain tissue (for example the bone range is 1.3-2.4%\(^{\circ}\)C). In addition, the range of average sensitivity from tissue to tissue is also wide (1.44-2.0%\(^{\circ}\)C). Estimating the sensitivity in the range of 30-43\(^{\circ}\)C narrows the range of sensitivity from experiment to experiment for a certain tissue. For example, the worst range calculated (fat) is 1.3-1.8%\(^{\circ}\)C. Also, the variability from tissue to tissue is improved to 1.3 to 1.7%\(^{\circ}\)C (average sensitivity). Muscle, bone, and kidney have a sensitivity of about 1.7%\(^{\circ}\)C, whereas fat and liver have lower sensitivity (1.4 and 1.3%\(^{\circ}\)C). In the Matsumoto et al. paper [100], the sensitivity for excised liver was 1.2%\(^{\circ}\)C evaluated in the range of 30 to 43\(^{\circ}\)C.
°C. This value is in good agreement with the results of this paper.

The average signal sensitivity for rabbit tissues varied from 1.18 to 1.59 %/°C. Liver showed the lowest sensitivity (same result seen in the dog study). Generally, the sensitivities in rabbit are lower than those in dog (except for the case of fat). Muscle and liver shows small variability from animal to animal.

The sensitivity is a very useful quantity that can be used to measure temperature during hyperthermic treatments where the goal is to elevate the temperature from 37 to 43 °C for 30-60 min [7]. Thus, to establish this temperature elevation (6 °C), depending on the hyperthermic modality (ultrasound, laser, microwaves, RF currents, etc.) the energy should be controlled until the intensity drops by 6 °Cx1.42 %/°C=.085 or 8.5 % (considering a rabbit kidney treatment).
6.5 Monitoring of necrosed volume during ultrasound surgery.

The purpose of this study was to present imaging techniques using MRI to monitor the necrosis of tissue or tumors during ultrasonic exposures. This was first demonstrated by Hynynen et al. [101] in vivo muscle. Additional results are presented from further studies in muscle, kidney, and brain. The size of the lesions produced were measured using MRI. Previous studies can be found in Hynynen et al. [10], Hynynen et al. [92], Darkazanli et al. [102], Hynynen et al. [103], and Hynynen et al. [104].

Proton density and $T_2$ weighted images were obtained. For the proton density weighted images $TR=2000$ ms and $TE=16$ ms were used. For the $T_2$ weighted images $TR=2000$ ms and $TE=60$ ms. The slice thickness = 5 mm, slice interspace = 1.5 mm, NEX = 0.5, and the matrix was 256x128. The above techniques provide good contrast between necrotic tissue and normal tissue.

The system described in section 6.2 was used with a transducer having a frequency of 1.656 MHz and a radius of curvature of 8 cm (diameter = 10 cm).

Fig. 6.20A shows lesions in a rabbit using a proton density weighted image. Fig. 6.20B is the corresponding image with $T_2$ weighted imaging. These images were used to obtain the diameter of the lesion at different powers and pulse duration. Fig. 6.21 shows axial images in a rabbit's muscle with proton weighted imaging. These images were used to obtain the lesion length. Fig. 6.22A shows
Fig. 6.20 A) Proton density and B) $T_2$ weighted image of lesions in rabbit muscle (at different power levels) used to measure the diameter of the lesion.
Fig. 6.21 Proton density weighted image (axial) of lesions in rabbit muscle used to measure the length of the lesion.
Fig. 6.22 $T_2$ weighted image of lesion A) in rabbit kidney, and B) in rabbit brain used to measure the diameter of the lesion.
lesions using $T_2$ weighted images of a rabbit kidney and Fig. 6.22B shows lesions in the rabbit brain. Finally, Fig. 6.23 shows the ultimate goal of this study. In this figure multiple pulses were applied to necrose a large volume of tissue (rabbit muscle). Totally, nine (9) pulses were applied of 30 s pulse duration and 30s delay between the pulses. The necrosed volume was 17 mm x 15 mm.

Fig. 6.23  Lesion in rabbit muscle created using 9 pulses (30 s pulse duration and 30 s delay between pulses).
CONCLUSIONS

The concept of thermal dose is a useful tool in evaluating the thermal effects of ultrasound. By knowing the target thermal dose for a specific application parametric studies can be performed for selecting transducer parameters (frequency and F-number), and sonication parameters (pulse duration and power). In addition, the effect of tissue properties such as perfusion and attenuation can be evaluated.

In this document, three different applications were studied. In the first application the goal was to deliver 60 min of thermal dose in a certain region using multiple pulses, without causing damage to the surrounding tissue (near-field). Thus, the dose in the near-field had to be smaller than 60 min. It was found that by using delay between pulses of 20 s, the near-field heating was avoided. Pulse durations smaller than 5 s resulted in decreased near-field heating. The F-number of 1 and frequency around 1-2 MHz is recommended for reducing the near-field heating to safe levels. The same approach can be used when evaluating the near-field heating when multiple pulses are used for ultrasonic surgery. In this application the goal will be to deliver 240 min of dose in the boundary of the target volume and thus the dose in the near-field must be less than 240 min.

A very important issue when applying multiple pulses is the uniformity of thermal dose in the focal layer. The goal in this study is to achieve thermal dose between 30-60 min. Using this goal the correct spacing between the pulses in the
axial and radial direction was found as a function of frequency, F-number and pulse
duration.

The most important study is to predict the size of the necrosed volume during
high-intensity ultrasound. The goal in this application is to find the boundary where a
threshold dose for necrosis is obtained (240 min for muscle). Using this boundary the
size of the necrosed volume was found. The size increased with power, pulse
duration, and F-number and decreased with frequency when the power intensity was
kept constant. Perfusion independence can be obtained by using pulse of 5 s or
shorter.

The general idea of finding the necrosed volume was applied to a special case
where a highly-perfused tissue seated a few cms deep was sonicated. The goal in this
study was to avoid necrosis in the surrounding tissues (i.e. the thermal dose had to be
smaller than 240 min in the surrounding tissues). It was found that by using a
transducer with F-number of 0.8 and frequency of 1 MHz necrosis was localized in
the sonicated layer (in this case kidney). The power levels to avoid in the other
tissues were obtained as a function of frequency and pulse duration.

Magnetic resonance imaging can be used effectively to monitor changes in
tissue when high-intensity ultrasound is applied. The signal sensitivity to temperature
was evaluated for tissues in vitro (from dog and rabbit) and the sensitivity of 1.2-1.7
%/°C was found.
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