ULTRASONIC APPROACH TO NONINVASIVE TEMPERATURE MONITORING DURING MICROWAVE THERMOTHERAPY

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Abstract

Microwave thermotherapy (MT) is an oncological treatment. At present the invasive thermometer probes are clinically used for temperature measuring during an MT. Any invasive handling of tumors is of high-risk. A new possible method of noninvasive monitoring of temperature distribution in tissue has been developed. An MT treatment of the experimentally induced pedicle-tumors of the rat was prepared. For 100 rat samples a strong correlation between the mean gray level in the ROIs in the ultrasound pictures and the invasively measured temperature in the range 37-44 °C was found. The correlation coefficient of the mean gray level and the invasively measured temperature is 0.96±0.05. A system for representation of changes of spatial temperature distribution of the whole tumor during MT is presented.

Keywords

noninvasive temperature measurement, ultrasound, texture analysis, hyperthermia, oncological treatment, 3D temperature monitoring

1. Introduction

The microwave thermotherapy (MT) has been an important treatment in oncology in recent years. It has been used in chemotherapy, surgery, biological therapies, breast cancer therapy, prostate cancer therapy, radiotherapy, etc. The basic technical principle of MT is a temperature increase in a treated area of tissue for a specific time interval and temperature range. This could be accomplished by equipment based on a regulation loop using an ultrasonic or electromagnetic field. The equipment for MT consists of a high-frequency generator, applicator, regulation PC, and thermometer. The thermometry is a very important part of the MT. For an effective MT it is necessary to maintain the temperature distribution in treated tissue in a range approximately 42÷45 °C. If the temperature inside the area of treatment drops below 42 °C, there will be no intended effect. On the other hand if the temperature exceeds 45 °C, the "healthy" cells will be also affected, not only the tumor's ones. Such an effect is not intended. Of course, it is important to monitor the temperature distribution, at least, in the whole area of treatment. Sometimes temperature monitoring outside the area of treatment is needed to prevent the "hot spots" damages in tissue.

At present the invasive thermometers are clinically used for MT purposes, although the invasive methods for temperature measurement in oncology is relatively risky and also has several technical disadvantages. The most important problem in the biological area is probably the increase in the risk of metastases formation. Whenever invasive probes penetrate through a catheter into the tumor, there is a possibility of carrying of tumor's cells from the tumor to the surrounding tissue or even to the blood or lymph system. Subsequently the metastasis could be created. There are also several technical problems. The incomplete space cover of temperature measurement is one of them. Because invasive thermometers have at most 12 channels, the temperature distribution inside the treated area could be measured only in these points. The temperature in the rest of the parts has to be estimated. The estimation is aggravated by the complexity of the tissue order and by the complexity of the applicator's aperture. In some cases such types of monitoring could be insufficient.

All described disadvantages are irrelevant for noninvasive techniques of temperature distribution measurement in the whole area of treatment. There are more physical principles, which could be used for temperature measurement in a range up to 45 °C. The use of the ultrasound has all of the benefits of noninvasive techniques and heads this group from more points of view. It assures sufficient spatial resolution for MT purposes (vs. dielectric properties measurement), the monitoring of temperature distribution is possible in a much more extensive area than for invasive techniques. The ultrasound penetrates the tissue in sufficient depth (vs. infrared and microwave techniques) and represents no burden to a patient (vs. X-CT). Interaction

between EMF therapy part and ultrasonic diagnostic part is minimal (vs. dielectric properties measurement, MR). The purchase and running costs are relatively low (vs. MR) and there is no problem to transport the ultrasound equipment to a patient or another therapy equipment (vs. MR).

2. Methodology

The goal of the project is to develop a method, which enables a monitoring of changes in temperature distribution during MT treatment, in temperature range starting at normal temperatures of the human body up to 45 °C. A device based on this method provides information about temperature distribution inside the treated area of tissue.

2.1 Physical background

The speed of a longitudinal ultrasound propagation in a liquid medium could be described by the equation

$$c = \sqrt{\chi/(\rho\varepsilon)}, \tag{1}$$

where c is speed, χ is Poisson's constant, ε is isothermal compressibility and ρ is the density. The advancement of equation (1) could be simplified for example for water to

$$c \sim 1403 + 5T + \text{higher order polynomial}, \tag{2}$$

where c is the speed and T is temperature. Several experiments have confirmed that the temperature dependency (around 40 °C) of ultrasonic speed is a monotone function of temperature in soft tissues. The sensitivity was determined $0.5 \div 4.0$ ms^{-1}.°C^{-1}.

For medical diagnostic purposes a reflection measurement method is used. A reflected signal received by a piezoelectric probe depends on the shape of the emitted signal and on the distribution of tissue (medium) the probe is scanning. There are more, temperature dependent, ultrasonic parameters of the tissue, which affect the signal, e.g. scattering, attenuation, speed of signal, reflection coefficient, etc. All these parameters take part on construction of a B-mode image. If the linear temperature dependency of the speed is dominant among mentioned parameters, the B-mode image will keep similar dependency, for example, in its texture parameters.

The reflection coefficient is defined by

$$r = \left(\frac{Z_{a2} - Z_{a1}}{Z_{a2} + Z_{a1}}\right), \tag{3}$$

where r is the reflection coefficient and Z_{a1},, Z_{a2} is an acoustic impedance of medium *1* and medium *2* representing the acoustic transition in medium. Because the acoustic impedance is defined by

$$Z_a = \rho c, \tag{4}$$

the impedance is temperature dependent and subsequently the reflection coefficient is temperature dependent too. The temperature dependency of other parameters is more complex and some of them are difficult to be described by an analytical equation. One way could be to use a statistical approach for each parameter description separately. Other way, used in this project, is the statistical approach to parameters as a common group, a B-mode image processing.

2.2 Biological material

2.2.1 Animal and tumor model

Experiments were performed with the R3327-AT1 subline of the Dunning prostate tumor (Isaacs and Coffey 1983) which represents an anaplastic carcinoma with a labeling index (LI) of 7.0 ± 0.5 and 8.8 ± 3.7 percent measured with a flow cytometry and histology, respectively, S-phase duration (Ts) of 8 h, a potential doubling time (Tpot) of 4.7 days and a cell loss factor of 15% (Lohr et al. 1993). In addition, this subline has a low metastatic potential and is hormone independent. Tumor oxygen tension as examined by ^{19}F nuclear magnetic resonance spin-lattice relaxation rate (R1) of perfluorocarbon (PFC) emulsion revealed a size dependent development of a generalized central hypoxia (Mason et al. 1999). Nevertheless, the degree of hypoxia is not sufficient to induce a central necrosis as is often seen in the more rapidly proliferating rodent tumors.

2.2.2 Surgical procedure

Fresh pieces of tumor tissue (~ 2 x 2 x 2 mm^3) were transplanted into a dorsal skin flap pedicle (Hahn et al. 1993) of an anesthetized male young adult (180 g) Copenhagen rats (Wiga, USA). Fresh material for implantation was obtained from tumors grown from a cryopreserved stock, that was maintained as a first passage of the original tumor. Briefly, animals were shaved in the neck/shoulder region. A flip of skin was raised in this area and held in position with nontraumatic curved bulldog clamp. A 3 cm incision was made through both layers of skin using the curved edge of the bulldog clamp as a guide. Cut edges of the skin were joined by surgical thread. After 10 days, when skin had sufficiently recovered the distal end of the pedicle was served and pieces of tumor tissue were inserted into the lumen. Served end was closed with a wound clip. Hyperthermia was started when the tumors reached a diameter of 18±1 mm. All animal experiments were performed under general gaseous anesthesia using a mixture of halothane (1%), oxygen (33%) and nitrous oxide (66%). Animals were maintained according to the guidelines established for laboratory animals by the German government.

2.3 "Standard" part of the technical equipment

The laboratory made MT equipment (Fig. 1) has its own intelligent regulation loop. Main parts of the loop are

a microwave generator, an MT applicator, an invasive thermometer, and a regulation PC.

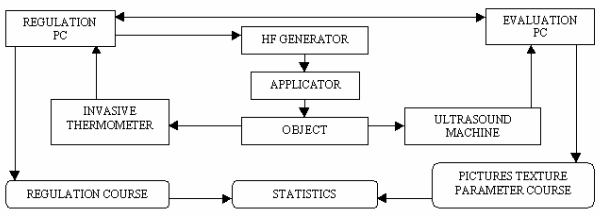

Fig. 1 Scheme of the experimental MT equipment

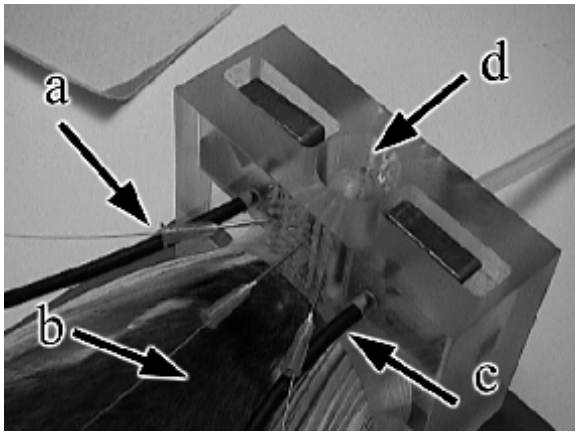

Fig. 2 Thermometer probes: thermometer probe (a), rat (b), coaxial cable (c), tumor (d)

The generator has 8 channels with maximal power output 50W on 915 MHz. A microwave applicator is the device where microwaves meet and heat the material to be processed. The applicator used in this project is enabled also for MRI experiments. It is connected to 2 channels with no mutual phase shift. For temperature measurement, the optical thermometer Luxtron 3000 was used. Four optical channels were led through the wall of the applicator inside the tumor (Fig. 2).

The optical thermometer guarantees a minimal influence of the EMF on the temperature measurement. The regulation computer closes the loop. It is connected to the thermometer and to the generator. Regulation software controls the output of the generator according to the actual data obtained from the thermometer and according to the assigned temperature/time course. The temperature/time course could be designed before the experiment starts. The 5s-regulation step is short enough, because of the temperature inertia of tissue.

2.4 Parallel "noninvasive" part of the technical equipment

The "noninvasive" part is connected parallel to the invasive thermometer. The aim of this part is to produce information about changes of temperature distribution in the scanned medium and to provide this information to the regulation computer or together with the thermometer data for later statistical analysis. It consists of an ultrasound machine (Acuson Sequoia 512, 15L8 probe-13MHz) and an evaluation PC. Evaluation computer is able to capture B-mode images from the ultrasound machine. The capturing process is controlled either by the regulation computer or could be executed manually on the evaluation computer. The ultrasound probe is fixed to the applicator (Fig. 3). For 3D measurements a special tool has been developed (Fig. 4). The image analysis is evaluated after the whole series of images is stored on the disc or a simple analysis and displaying of its results is processed during the experiment.

2.5 Ultrasound data processing

The image registration helps to eliminate changes of the ROI's texture parameters caused by the movement of the ultrasound probe during an experiment. All ROIs selected in the first picture of the series delimit the same texture area of the new picture after registration. For this project the chamfer matching registration was selected.

The objective of the data processing is to determine the distribution of temperature changes in tissue using ultrasound image analysis. To determine whether any texture parameter correlates with the temperature, it is necessary to eliminate all other possible influences on texture as much as possible. The image processing is organized into the following steps:

a) image registration,
b) regions of interest (ROI) selection,
c) image segmentation,
d) texture parameters evaluation,
e) results interpretation.

ROIs could be projected from previous image after the registration is finished.

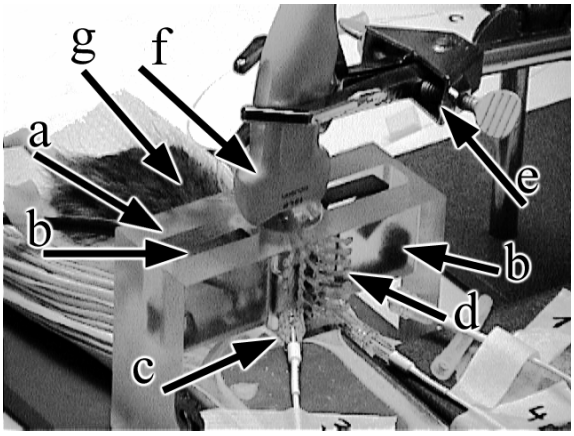

Fig. 3 The MT applicator and an ultrasound probe: skeleton of an applicator (a), EMF antenna (b), thermometer probe (c), stack for a tumor (d), laboratory holder (e), ultrasound probe (f), rat (g)

The image segmentation parcels an image according to the contained textures. There are different transfer functions between the texture parameter and the evaluated temperature for different types of tissue. The segmentation

enables you to select the proper transfer function for each type. A simple dynamic threshold algorithm suffices for segmentation of tissues used in this project. It is self-evident that a more robust method will be indispensable for general use.

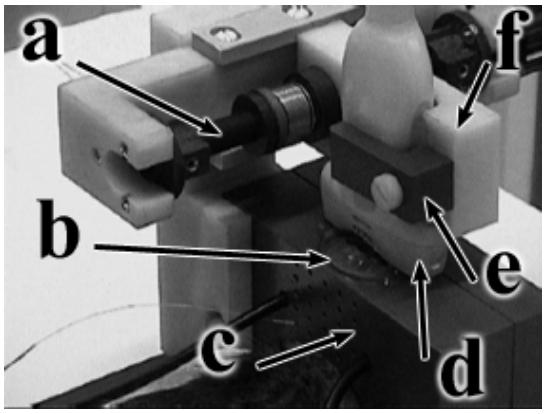

Fig. 4 The 3D positioning device for an ultrasound probe: screw rail (a), contact gel (b), applicator (c), ultrasound probe (d), pressing arm (e), probe holder (f)

The first order gray level characteristics, the first order gradient characteristics, cooccurrence matrix and run-length matrix statistics (texture parameters) were evaluated from the obtained ultrasound images. For gradient characteristics, cooccurrence and run-length matrix a $\pm 3\sigma$-normalization was used to eliminate their mean gray scale value dependency.

2.6 Design of experiments

Two main groups of experiments were done: 2D and 3D. The goal of 2D experiments was to answer following questions:

1. Are there any texture parameters dependent on temperature of the scanned tissue?
2. Are these parameters stable owing to the temperature?
3. How does the blood supply change the value of the parameters?

For the MT regulation a temperature course was designed (Fig. 5). For each temperature interval five ultrasound pictures were captured. Pictures were captured also in the period of cooling down due to the nature temperature of the used tissue. Points 1-3 were executed in-vivo (pedicle tumors). The pedicle was tied up and then processed once again for point 3.

The goal of 3D experiments was to verify the continuous relations among the evaluated temperature distribution in discrete slides. The same temperature regulation course was used, as in the previous case. At each temperature interval images for the whole 3D object (50 slides with 1mm span) were captured. To keep the spans constant for each 3D object a special positioning device was developed and used.

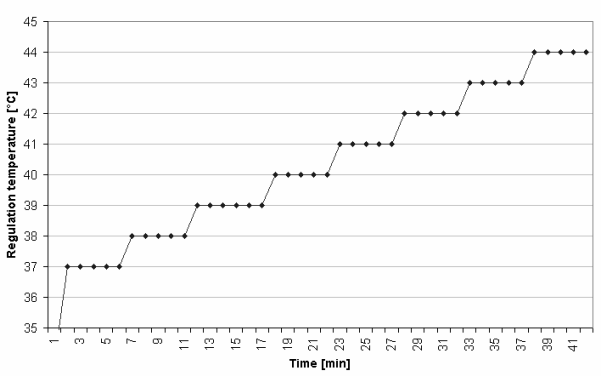

Fig. 5 Temperature/time regulation course used for experiments

The temperature was measured during all experiments with 2÷4 invasive optical thermometer probes. The measured temperatures were used for the MT controlling and for statistical evaluation with the ultrasound data.

3. Results

3.1 2D in-vivo experiments

In-vitro experiments, performed with pork liver phantoms heated in a water bath, showed a strong correlation between the mean gray scale value of ultrasound pictures and the temperature of heated phantoms. On the base of the results of these experiments the in-vivo experiments were done.

For 60 rats three different ROIs (100x100 pixels) have been selected in each ultrasound image of a tumor area. Four of sixty series were not evaluated, because of the devaluation of images by technical problems during the experiment (failure of regulation, large necrosis of used tumor,...). A strong correlation between the mean gray scale value in the ROIs in the ultrasound pictures and the invasive measured temperature in the range 37÷44 °C was found. The correlation coefficient of the mean gray scale value and the invasively measured temperature was $r=0.96\pm0.05$. The dependency of the evaluated temperature to the normalized mean gray level was a linear function, with a starting point at 37.00 ± 1.18 and gradient 0.94 ± 0.23. The next best parameter was the mean gradient. The correlation of the mean gradient and the invasively measured temperature was $r=0.74\pm0.21$. All other parameters did not show any higher correlation with the temperature.

To get information about the temperature distribution in the whole scanned XY area, every image of the data series was parceled (12x12 pixels) and in each region the mean gray scale value was evaluated. The matrix of results were used for pseudo-color coding of grayscale B-mode images.

Figures are available at **http://www.cbmi.cvut.cz/en/**.

3.2 3D in-vitro experiments

Four pork meat phantoms were used for an MT treatment. Using a special positioning device (Fig. 4) a series of 50 images were obtained for each phantom. For evaluation, the edge images were not used because of different sizes of phantoms. 3D experiment approved the presumption of continuous relations among the evaluated temperature distribution in discrete slides (Fig. 6). The relative changes are almost constant for the same temperature difference. This corresponds with the linearity of temperature dependency of the mean gray scale value and it was observed in the whole data volume. Information about the temperature changes in the whole volume of treated area was obtained.

4. Discussion

This method was tested on pork meat phantoms in-vitro and prostate tumors in-vivo. Although the change of the mean gray scale value for 1 °C temperature change was the same for both tissues, the texture parameters are expected to vary in their changes for 1 °C for different tissue types. Therefore, a base of transformation functions texture parameter-temperature has to be built. Based on the picture processing with a correct transformation functions predication, the temperature changes in the scanned area are measurable.

To monitor the absolute temperature distribution in tissue and not only the relative temperature changes, another system could be used to determine the native temperature distribution before the therapy starts. For these purposes the MRI techniques seem to be the most suitable. After the native temperature distribution is once determined, an ultrasound method uses the MRI results as a reference, and therefore, the temperature distribution evaluated by an ultrasound method is an absolute temperature distribution. A method for MRI and ultrasound pictures 3D registration ensures the proper use of MRI results.

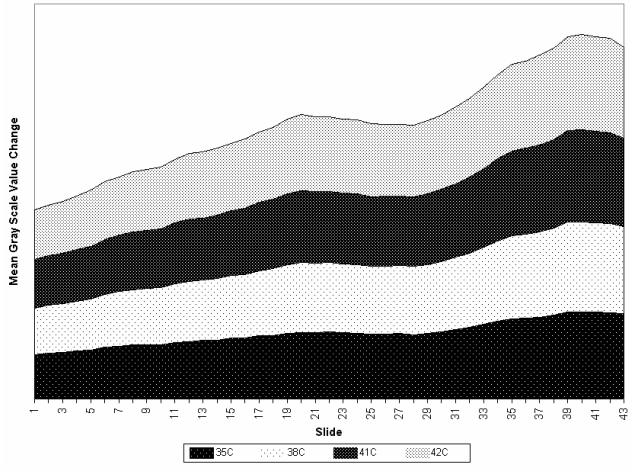

Fig. 6 Relations among the mean gray scale values of slides of a 3D object for different temperatures

5. Conclusions

The results show a very good possibility of using the ultrasound B-mode images processing method as a base for the temperature monitoring during MT. The possibility of noninvasive measuring of temperature distribution in the whole area of treatment enables a much more accurate and safer controlling of the MT then by invasive techniques used in clinical praxis nowadays. Even faster development of the therapy part is expected, which would use all benefits brought by a 3D-measurement method with a high spatial resolution.

Acknowledgement

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BOOK REVIEW

V. Moucha, S. Marchevský, R. Lukáč, C. Stupák:

DIGITAL FILTERING OF IMAGES / ČÍSLICOVÁ FILTRÁCIA OBRAZOVÝCH SIGNÁLOV

Edičné stredisko VLA Gen. M. R. Štefánika, Košice, 2000, ISBN 80-7166-036-1, 369 pages, 134 figures, 91 tables

The book "Digital Filtering of Images" covers main areas of image processing theory with emphasis on digital filtering of images, noise suppression and noise detection. Particularly, representation of images, linear filtering of intensity images, nonlinear filtering of intensity images, multidimensional image filtering are discussed in detail.

The text is divided into thirteen chapters: A Model of an Image and Noise, Wiener Filters, Kalman Filters, Median Filters, Detectors of Impulses, Composition Filters, Weighted Median Filters, LUM Filters, Filters Based on Permutation Theory, Neuronal Filters, Fuzzy Filters, Filtering of Color Images, Filtering of Dynamic Images.

In the first chapter, images and various types of noise are modeled for the later use in linear and nonlinear filtering. The second chapter describes a classical Wiener filter in all representations. The Wiener filter is thoroughly discussed including its 2D version and relation with an adaptive LMS algorithm. The third chapter closely follows the previous text and deals with 2D Kalman filters. Nonlinear applications are introduced by median filtering discussed in the fourth chapter. The main principle of median filters is elementary but is extended by several modifications here. It includes order-statistics, hybrid and morphological median filters, recursive and fuzzy median filters. Advanced local filtering techniques are preceded by description of impulse detectors in chapter 5. The detectors are based on local statistics and are used to decide on the presence of impulse noise. Chapters 6 to 11 describe less published but effective filters. The discussion begins with composition filters with fast implementation of genetic algorithms and proceeds with weighted median filtering as an optimal order-statistics technique. Smoothing Lower-Upper Middle filters represent another modification of weighted median filters and are described in Chapter 8. Permutation theory is used to design estimating filters based on spatial and/or time information in Chapter 9. Theory of artificial neural networks and its use for image processing is briefly discussed in Chapter 10. Chapter 11 deals with another interesting and effective implementation - fuzzy filters. Finally, last two chapters consider images in their multidimensional representation for color imaging and time-sequences.

A strength of the book is in thorough description of particular filters including their realization. Also, simulation and tests were run on standard images (Lena, Bridge, Rectangulars, etc.) and the results were documented in a number of figures. Noisy environment was simulated by additive and impulse noise both correlated and uncorrelated. Thus, main characteristics of filters were revealed.

The book can be recommended to master's and doctoral students of radio-electronics at technical universities. Moreover, researchers in the field may find the textbook as a comprehensive source of image processing algorithms for noise suppression. For easy use and study, it contains a comprehensive list of abbreviations, a list of used symbols, detailed index, and a list of 335 references.

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The book can be ordered at **lukacr@ccsun.tuke.sk**.
Executive editor