HLT-03 DUTy





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1 Executive Summary

The overall aim of this project was to start the development of a metrological infrastructure to support ultrasound dosimetry and bring treatment planning more in line with other longer established treatments, e.g. radiotherapy. It has developed i) definitions of the most important dose quantities within an overall framework relating exposure and dose to free-field quantities, ii) measurement methods appropriate for calibration and research laboratories and hospitals, and iii) new modelling capabilities to support treatment planning and risk assessment. The measurement infrastructure within European NMIs has been significantly broadened and the scientific findings have been widely disseminated, including to the IEC where five new therapeutic ultrasound standards have been published or initiated.

The Problem: Ultrasound is currently used to treat a range of conditions. Over the last decade there has been a dramatic increase in the use of High Intensity Focused Ultrasound (HIFU) for treating cancer, stroke and bone repair. The main side effects of HIFU exposure to tissue are: ablation, caused by temperature increase and cavitation. Currently the techniques required to support the accurate application of a specific therapeutic dose to tissue do not exist, preventing manufacturers and clinicians from calculating the precise amount of ultrasound required for a particular therapy. This may result in over or under treatment of tissue and lead to patient harm, it also prevents the consistent implementation of new techniques and the creation of personalised treatment plans.

The Solution: To address this problem, this project supported the development of appropriate dosimetry through the development of validated measurement techniques, reference standards and modelling methods for quantifying exposure to ultrasound and the dose to tissue. The new dosimetric framework will support treatments and allow health outcomes from different treatment centres to be correlated.

Impact: Wide dissemination of the scientific outputs is an essential aspect of developing the international consensus necessary to develop standards, which in turn will encourage the development of next generation therapeutic devices. Overall 49 scientific papers have been published or accepted and there have been 69 presentations at conferences. There has been substantial impact on standardization in IEC TC87 (Ultrasonics) and IEC SC62D (Electromedical therapeutic equipment). Three IEC Standards for High Intensity Therapeutic Equipment have been published which are harmonized within the Medical Devices Directive and referenced by the US Food and Drugs Administration (FDA) amongst others: as such they directly affect manufacturers of all sorts of HITU equipment. Two new IEC projects have also been initiated by project partners Stimulated by this project, the UK and USA National Committees have submitted two New Work Item proposals related to therapeutic ultrasound to IEC TC87 (one jointly led by NPL on acoustic holography and field modelling; the other on high pressure field measurement). Another proposal on calibration of HITU hydrophones to be led by PTB is currently under consideration.

This project has enhanced the European measurement infrastructure for therapeutic ultrasound which have been disseminated to the instrumentation, clinical, standards and research communities and are already starting to be used by the project participants and stakeholders. NPL, PTB, HoMe and NIM have already carried out measurement services for five therapy companies and numerous other enquiries have been received.

The long term beneficiaries of this project will be manufacturers, doctors and patients. For manufacturers and regulators the benefits will be a clearer route for bringing new modalities to market and help to establish more homogenous global regulatory and purchasing requirements. For doctors and healthcare providers there should be an increased range of reliable therapies available and greater information to guide equipment procurement and to underpin patient care; these should help reduce, or at least control, healthcare costs for relevant conditions. For patients, improved therapies will lead to better disease management and improved quality of life; including less invasive cancer treatments, with fewer side-effects and shorter recovery times.



2 Project context, rationale and objectives

Ultrasound is a mechanical wave disturbance at frequencies greater than 20 kHz although, for most medical applications, the frequencies used are above 0.5 MHz (500 kHz). Under some conditions of acoustic power, pressure and intensity, the interaction of the wave with the tissue brings about physical or chemical changes in the medium which may be either reversible or irreversible. For more than 30 years ultrasound has been widely used for a range of medical applications such as physiotherapy and lithotripsy. The market for 'ultrasound ablation' equipment in the EU (which includes ultrasound used for phacoemulsification, lithotripsy, cancer therapy, gynaecology, general surgery and cosmetic/aesthetic uses) was worth about €360 million at the start of the project, and is forecast to reach €870 million by 2019 at an annual growth rate of 9.3%. Globally, in 2009, the value was about €1.32 billion with a predicted growth rate of more than 11% (Report A145, MedMarket Diligence LLC, 2010).

The interest in ultrasound as a surgical and therapeutic tool in its own right has grown considerably in recent years and much of this growth has been due to the use of high intensity focused ultrasound (HIFU) for tissue ablation in the treatment of cancers and conditions such as benign prostate hyperplasia (BPH). HIFU is focused within tissue with the intention of generating intensity levels sufficient to raise the local tissue temperature above 55°C. Although first tested many years ago, recent developments in materials, computing and other technological advances have only now allowed HIFU to be exploited within the medical mainstream. HIFU can be delivered using intravascular transducers (for example to treat atrial fibrillation in the heart) and there are even two commercial HIFU systems for the non-invasive treatment of brain tumours and conditions, such as essential tremor, through the intact skull.

Tissue ablation by HIFU is perhaps the most relevant new application, yet it is just one among many new treatments of tendon injuries using lithotripter-like devices, stimulation of bone repair by low intensity ultrasound, ultrasound-induced haemostasis, pain relief, fat removal for cosmetic purposes and targeted delivery of drugs through the localized destruction of carrier particles by ultrasound. A series of reviews can be found in Ultrasonics 48 (2008) "Ultrasonics Special Issue: Therapeutic Ultrasound".

The word "dose" commonly takes one of two meanings: the amount of something administered, usually a medicine; or the energy deposited by the absorption of ionising radiation, such as X-rays or electrons. The term 'ultrasonic dose' has never gained clear definition and usage in the context of the interaction of ultrasound with tissue. The lack of such a definition has led to confusion in the description of the conditions governing the treatment of the patient or, more generally, the interaction with tissue. For example, it is not uncommon for physiotherapists to use the word 'dose' to refer to the acoustic output, as indicated by the acoustic power in watts, or by the output intensity in watts per square centimetre displayed on the ultrasound equipment.

Nevertheless, the ability of some new therapies to produce such acute effects within tissue (HIFU can boil tissue around the focus within seconds) drives an absolute requirement to ensure that the treatment is delivered to the correct level and at the correct site. This in turn means that accurate methods of predicting the dose and monitoring performance are required. The need is not just for HIFU, but it is echoed for all ultrasound therapies. In soft-tissue physiotherapy, operators typically select between a 1 MHz probe for deeper injuries, and a 3 MHz probe for shallower injuries, perhaps also selecting a level for total power or a beam-average intensity. Surveys have shown that a high percentage of ultrasound physiotherapy systems either produce no output or an output which differs substantially from the indicated setting.

Unlike ionizing radiation, therapeutic ultrasound applications do not incorporate standardized, comparable dose concepts that are underpinned by traceable measurement. This lack of a proper knowledge of dose makes it impossible to determine dose-response curves and to arrive at robust and individualized treatment plans. Treatment planning, as it exists, is founded on the individual therapist's experience and it is largely based on time and intensity measured in free-field conditions, not on the sound field expected in tissue. Consequently, almost all treatments with ultrasound are essentially empirical and it is impossible to compare the effectiveness of different systems or the suitability of different conditions to treatment. Traceable dosimetry will enable the comparison of data from trials, research and routine treatments across Europe providing a large and coherent body of evidence for understanding the effectiveness of treatments in terms of dose and patient effect.

In the absence of standardised, traceable, dose quantities, international standards are based on measurements of the ultrasound field emitted into water (often called 'free-field' quantities). European National



Measurement Institute (NMIs) have led the world in terms of metrology, being responsible for a number of novel developments impacting directly on patient safety and clinical efficacy. Partly due to the effort of NMIs, the metrology for therapeutic ultrasound fields under free-field conditions in water has advanced during the last years. However, it still requires substantial development in order for therapeutic applications to be fully exploited. Acoustic output power radiated into water can be measured beyond 150 W in the frequency range 0.5 MHz to 3.0 MHz with an accuracy of ±5 % and the spatial distribution of pressure in these fields is measurable (again in water) with an accuracy of ±10 %. However, for interaction with tissue, it is not yet even clear which field quantities are most appropriate. The temperature rise in the treated region can be measured using magnetic resonance (MR) thermometry or by direct measurement with thermocouples. The highly destructive nature of these fields remains an issue hampering measurements under clinically relevant conditions. As such, theoretical modelling will play an essential role in characterising the dose to tissue. Recent advances in computing power have enabled the prediction of nonlinear propagation of ultrasonic pressure waves in 3D domains. There are nevertheless challenges that remain for highly nonlinear fields, where many harmonics need to be retained in the solution, and for domains that are hundreds of wavelengths in size. The difficulties are greatly exacerbated when the medium properties change significantly as a result of heating or other interactions.

In ultrasound diagnostic imaging, two safety 'indices' - the Thermal and Mechanical Indices - are used. However, these involve many simplifications and compromises and assume a single, atypical tissue model. These indices are not suitable for any type of therapy quantification or planning. One quantity which is potentially useful for planning and has widespread use in literature (at least for HIFU therapy) is the 'thermal dose', which is more correctly called 'thermal equivalent time' or 'cumulative equivalent minutes'. This quantity relates the duration of exposure at one temperature to an equivalent duration at a different temperature: equivalent in the sense that it should achieve the same biological endpoint (often a specified fraction of cells killed or of malformed embryos). This quantity has dimensions of time and is therefore very different to dose quantities used in other types of therapy (which are usually based on energy deposition). Although it has been tested for times above about 1 minute, evidence supporting its appropriateness for short times at high temperatures is very limited and the accuracy of the true temperature of the exposed cells is questionable.

The development of an appropriate dose concept, and the metrology required to underpin it, are essential to achieve the ultimate goal of individually optimised therapy and to tap the full potential of ultrasound therapeutic methods. The lack of a proper knowledge of dose makes it impossible to determine dose-response curves for different kinds of tissue and to arrive at robust and individualized treatment plans. It is unlikely that ultrasound dose in the body during treatment will ever actually be measured, instead it must be calculated using models with known uncertainties and whose accuracy can be validated. This is also true for other forms of non-ionizing and ionizing radiation; dose determination for ionizing radiation is largely based on Monte Carlo simulation of the interaction between incident particles and the atoms in the medium. These models have become very refined over the years and are able to predict dose with an uncertainty of fractions of a percent. Monte Carlo techniques are not suited to ultrasound but it is clear that more accurate modelling is required to put ultrasound therapies on a similarly robust footing. Ultimately, modelling must simulate the propagation of a nonlinear wave generated by a complex non-symmetric transducer through inhomogeneous tissue-like media with properties that vary with temperature and over time. Also essential to this process is the specification of a method to determine the field input parameters for the model so that treatments can be planned in detail and therapeutic benefit maximised. This will improve the effectiveness of present therapies and enhance the development of future techniques. The ability to treat up to the tumour boundaries without damaging healthy tissue is often critical: outcomes improved noticeably in USA trials once FDA-imposed restrictions regarding maximum treatment volumes and preserved peripheral boundaries were relaxed in 2007.

The long term vision of this project was the establishment of a new harmonised global metrology infrastructure for ultrasound exposure and dose to tissue that will enable therapeutic ultrasound to deliver more effective and safer treatments across the spectrum of conditions from strains and minor fractures through to life threatening cancers.

This project intended to progress the state of the art by defining parameters, methods and protocols for ultrasound dose. This step-change started an underpinning metrological framework, which will facilitate ultrasound therapies to be placed on a similarly robust footing to ionizing radiation, and will eventually allow the dose-response of a range of ultrasound therapies to be properly understood and quantified. It will drive international consensus on the most appropriate dose quantities and develop the measurement techniques



allowing these quantities to be disseminated to the user communities. This project developed and evaluated potential laboratory measurement standards for dose quantities, including tissue mimicking materials and non-invasive methods which leave the propagation medium undisturbed. It also developed the modelling methods which will make it possible to apply the dose concepts more readily to a wide range of equipment and clinical situations, removing the barriers for exploitation of new therapy technologies. It built on the skills existing in the consortium and a number of recent developments such as k-space methods to advance the state of the art.

Specific objectives can be summarized as:

- 1. Development of a dose concept for therapeutic ultrasound;
- 2. Development of phantoms and measurement techniques for testing of dose concepts including the characterisation of measurement methods;
- 3. Development of test methods for the assessment of commercial machines and comparison of treatment effects and efficiency;
- 4. Modelling and validation of linear and non-linear ultrasound propagation through phantoms and anatomical structures;
- 5. Development of methods to improve the accuracy of the individual treatment including use of anatomical data.



3 Research results

A summary of the work of this project is given in the following sections 3.1 to 3.5.

3.1 Dose concept for therapeutic ultrasound

3.1.1 Introduction

Work carried out under this objective was important in starting to establish a common language for describing exposure and dose. The work has addressed consultation with stakeholders (3.1.2), a proposal of a framework for ultrasound dose (3.1.3), the development of a reference standard for ultrasound dose (3.1.4) and the evaluation of candidate quantities and comparison of measurements between project partners (3.1.5). Five related papers have been published.

3.1.2 Stakeholder input

The project started with a 2-day workshop on the topic of exposure and dose for therapeutic ultrasound which was organized by PTB in Heidelberg, Germany: 39 experts from 27 institutions in 9 countries participated. The participants covered a wide range of stakeholders: researchers, metrologists, regulators, clinicians, manufacturers and others.





In order to investigate the views of the wider therapy ultrasound community, a survey about exposure and dose for therapeutic ultrasound was brought online. The questions for the survey were discussed within the consortium in advance and the survey was advertised through the International Society of Therapeutic Ultrasound (ISTU) mailing list, by the Focused Ultrasound Foundation, by notices at the ISTU 2014 conference in Las Vegas, and by emails to personal contacts by the project team members. There were 123 responses to the survey and a paper summarizing the findings and titled "Equipment, measurement and dose – a survey for therapeutic ultrasound" has been submitted to the Journal of Therapeutic Ultrasound. A clear result from this survey is that more than 50 % of the respondents felt that they could not characterise their equipment satisfactorily, clearly demonstrating the need for further improvements in measuring devices, and for measurement guidelines. The set of charts in Figure 1 show some other important findings. The respondents expect that many aspects would benefit from a clear definition of dose for therapeutic ultrasound and, on balance, there is a preference for dose to be a spatially and temporally variable quantity which is related to absorption of energy in the exposed medium. Its role is more important in improving treatment than in addressing safety concerns.

3.1.3 Framework for ultrasound dose

A framework for describing exposure and dose has been developed which comprises four categories of 'quantity' to describe different aspects of an ultrasound treatment; these are summarised below. Two distinct uses for *in situ* and dose quantities in therapeutic ultrasound are identified:

- To permit comparison of the 'therapeutic power' of different pieces of equipment, or of different settings under reference conditions (i.e. where all properties are known exactly);
- To describe or predict effects in a particular sample of a particular medium (e.g. in the liver of an individual patient) where the properties may not be known precisely.

The first can be considered primarily of engineering or metrological use, and the second primarily of clinical use. They are clearly related, so it is important that not only the language used is common, but that the base definitions are also suitable for both.

The four categories are:

• Free-field (water) exposure quantities

These describe the ultrasound field in water and depend only on the source and the acoustic properties of water. Typically they are local pressures, local intensities, beam-shape descriptors etc.

• In situ exposure quantities

These describe the ultrasound field in a medium other than water. The *in situ* level depends on the source and on the acoustic properties of the medium. Essentially these quantities are similar to those used for free-field quantities (*eg* local pressures, local intensities, beam-shape descriptors).

• Dose quantities

These quantify the interaction of the ultrasound field with the medium. The magnitude of the dose depends on the *in situ* exposure level and on the acoustic and other physical properties of the medium. This category can be further separated into:

- instantaneous dose quantities (analogous to 'absorbed dose rate' in radiotherapy, quantifying the interaction before the properties of the medium change significantly);

- cumulative dose quantities (analogous to 'absorbed dose' in radiotherapy, quantifying an interaction which accumulates with time, and which is allowed to change the properties of the medium).

• Effect quantities

These quantify the change in the behaviour or properties of the tissue. The size of the effect depends on the dose and the dose-response of the tissue- (*eg* lesion volume rate; cell surviving fraction; the rate of production of a specified bio-marker).

Within this framework, two definitions for ultrasound dose have been proposed:

Absorbed ultrasound dose rate: the rate per unit mass at which energy is deposited by absorption of the acoustic wave in a specified medium. This is an instantaneous dose quantity. Local energy deposition will of course be strongly dependent on the *in situ* intensity, but is not dependent solely upon it. Hence, this is defined



in terms of energy deposited and not in terms of *in situ* intensity, nor of the square of the *in situ* pressure. It is a quantity which may vary with time at any location, but a case of special interest is the value immediately after the start of insonation when, in the absence of other significant energy storage mechanisms, it is proportional to the rate of change temperature at that point.

Absorbed ultrasound dose: the energy per unit mass which is deposited within a specified time by absorption of the acoustic wave in a specified medium. This is a cumulative dose quantity. Note that this is also defined in terms of energy deposited and not in terms of *in situ* intensity or of the square of the *in situ* pressure. It is a quantity which increases with time at each location, hence the need to specify the time. However it is not in general equal to the product of the time and the initial absorbed dose rate because energy losses must also be taken into account.

3.1.4 Reference standard for ultrasound dose

In radiotherapy, dose rates are traceable to calorimetric standards where the temperature increase is measured in a specified reference material and the absorbed energy is calculated from the temperature rise and the specific heat capacity of the absorbing medium. For one type of calorimeter used at NPL which employs graphite as the absorbing medium, temperature rises in the order of microkelvins; the region of interest is surrounded by vacuum chambers to minimise heat loss, and the high thermal conductivity of graphite ensures that the temperature rise in the region of interest is nearly uniform.

We set out to develop a reference standard for ultrasound dose based also on calorimetry. The challenges are rather different to those in radiotherapy since the calorimeter cannot be thermally isolated from the environment: this is because the ultrasound travels in water and the presence of vacuum or even gas in the propagation will reflect all the incident energy. Since tissue-like media absorb ultrasound energy guite strongly (about 20%/cm at 1 MHz increasing to about 50%/cm at 3 MHz), the thermal sensor must be quite close to the water. Moreover, most thermal sensors interact with ultrasound producing measurement artefacts like viscous heating. There is a high degree of spatial structure in an ultrasound field, meaning that the calorimeter should have good spatial resolution. Furthermore, it must also have good temporal resolution because high spatial gradients



lead to rapid changes in the rate of temperature increase, so long averaging times are not appropriate. However, the incident power is usually high for therapeutic ultrasound, typically from 1 W to several hundred Watts. This should give plenty of signal but has its downside because the rate of temperature rise may be several 10s of degrees Centigrade per second, potentially leading to changes in the properties of the absorbing medium. The medium should also be resistant to damage by acoustic cavitation.

The final configuration of the ultrasound calorimeter dose-meter used for this work has a thin-film thermocouple (TFT) of diameter 0.5 mm and thickness 12 μ m, sandwiched between two pieces of low-density polyethylene (LDPE) 1 and 10 mm thick (see Figure 2). The TFT was chosen to minimise viscous heating and conduction artefacts. Thermistors were rejected as commercially available ones were too thick (~0.2 mm) and attempts to make smaller ones were unsuccessful. Very fine wire thermocouples (12 μ m diameter) could potentially be used but are very fragile. LDPE was selected as the reference medium because i) it is stable, ii) has a history of use in ultrasound thermal phantoms as a bone mimic, iii) its thermal diffusivity (0.157 mm²/s) is close to that for water and soft tissues (meaning that its time response to transient insonation will be similar; iv) its thermal conductivity (0.33 W/m/K) and specific heat capacity (2300 J/kg/K) are lower than water but higher than most other polymers; and v) its acoustic impedance at 1.94 MRayl is also closer to water than many polymers, leading to lower reflection. The greatest difference from soft-tissues is that its attenuation coefficient is much



higher, resulting in larger temperature rise (and better signal-to-noise), but also attaching more importance to having the sensor close to the water interface. Gel-based materials were rejected as being too unstable, insufficiently reproducible and prone to cavitation damage. To reduce acoustic reflections from the back-surface of the LDPE sandwich, it is backed by a 31% glycerol solution instead of water which reduced the pressure reflection coefficient from 11% to 3.5%. The TFT output is connected to a low-noise Keithley 1081 pre-amplifier and then to a Keithley 2001 DVM, with the maximum sample rate being 50 Hz, as a sample time of at least 1 mains power line cycle is required to reduce noise. Thermal noise levels are typically 2 mK (rms) and the estimated uncertainty in the measured dose rate is +/-5% with major contributions from the heat capacity, curve fitting, calibration of the TFT and acoustic reflections. For comparison, the best achievable uncertainty when measuring intensity with a hydrophone in water is approximately 12-15%, mainly due to uncertainty in the sensitivity of the hydrophone.

The rate of energy absorbtion per unit mass of medium is given by:



$$\frac{dE(\vec{r},t)}{dt} = \rho C_v \frac{dT(\vec{r},t)}{dt}$$

For a wide beam in a weakly absorbing medium, the temperature increase is nearly proportional to time for several seconds and dT/dt is easy to determine by recording the change in temperature during the insonation period. In the more general case, high temperature gradients exist radially due to field structure and axially due to strong attenuation, which greatly complicates the process of determining dT/dt. Two approaches can therefore be used. When the energy deposition rate is high enough, very short exposures (even 10 ms, which is less than our sampling period) generate significant temperature rise that can be determined accurately by fitting to the temperature-time data that follows the end of insonation. When the energy deposition rate is lower and very short insonation times cannot be used, the data for a longer insonation time (τ) can be smoothed and then analysed a summation of a set of *n* shorter sequences each of length dn and delayed by dn

relative to the previous one. Standard curve-fitting can also be applied but this summed sequence approach avoids the need to make any assumptions about the expected form of the temperature-time variation, which is generally not known except approximately on-axis in the focus.

The summed sequence approach also provides a method to calculate an equivalent temperature rise for moderate insonation times when it is not desirable to carry out the measurement directly (generally because energy deposition rates are high and the heating that would occur would change the medium properties). By measuring the temperature evolution for a 0.1 s insonation followed by 10 s of cooling, the evolution for a 1 s insonation can be calculated by replicating the dataset 10 times, each delayed by 0.1 s, and summing as shown in Figure 3. Again, this makes no assumption about the expected form of the temperature-time variation; the post-insonation data provides all the necessary information.

3.1.5 Intercomparison

The aim of this activity was to evaluate measurement methods for dosimetry and exposimetry quantities by comparing the measurement results for three common quantities from three national laboratories. The general format was similar to a metrological comparison, with which NMIs are already familiar. The NMIs involved were INRIM (the pilot institute), NPL, PTB and TUBITAK.

A technical protocol was prepared and approved by all participants in the comparison. In the technical protocol, in addition to the timetable, two travelling transducers were specified i) Transducer 1: Piston like Transducer

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 f_0 = 2.01 MHz and ii) Transducer 2: Sonic Concepts focused bowl transducer f_0 =2.00 MHz and f_3 = 6.38 MHz. The protocol specified the nominal levels of ultrasonic power *P*, the corresponding electrical voltage U_s to apply to the transducers for the insonation phase, and the times for insonation, t_{ON} , and for zero signal applied, t_{OFF} . It was discovered before finalizing the protocol that the TMM was not able to withstand a despatch by courier. Therefore in the technical protocol the recipe and procedure for preparing a Gellan Gum (PHYTAGEL) based TMM was specified, in order to enable each laboratory to prepare the TMM for his own measurements.

From the results of the survey described in 3.1.2, three common definitions have been identified to be of high relevance and to be suitable for this work. Two are related to energy, namely the Applied Total Acoustic Energy (ATAE) and the Applied Total Electrical Energy (ATEE), and the third, the Thermally Equivalent Time (TET). The definition of TET has been adjusted to account for the fact that measurements were not carried out at 37 °C but at room temperature. TET was therefore defined with reference to a temperature increase of 6 °C (see equation below), rather than to a temperature of 43 °C. This redefinition is more appropriate to 'engineering' measurements and comparisons which are generally not carried out at 37 °C. For an initial temperature of 37 °C, the calculated TET is identical in both formulae. The laboratories have also determined $t_{t_{6}_{ON}}$ which is calculated in an identical way to $t_{t_{6}}$ except that t_{final} is set equal to t_{ON} (so that it includes only the TET delivered during the insonation period). In order to determine TET, it is necessary to know the time temperature profile T(t) at any point x in heated tissue (or TMM in this case).

ATAE =
$$E_{TOT_AC} = P_{AC} \times t_{ON}$$

ATEE = $E_{TOT_EL} = P_{EL} \times t_{ON}$
TET = $t_{+6} = \int_{t=0}^{t=t_{final}} R^{\left(6 - \frac{dT(t)}{\circ C}\right)} dt$ where $\begin{cases} R = 0.50 \text{ for } dT(t) > +6^{\circ}C \\ R = 0.25 \text{ for } dT(t) \le +6^{\circ}C \end{cases}$

n

Measurements results for ATAE are shown in part (a) of Figure 4 below; and results of TET measurements are shown in part (b).



Most of ATAE and ATEE measurements were consistent among the three laboratories, while TET measurements were not consistent, almost for every considered power level. This is probably due to the fact that the TMMs used for measurement were prepared on site at each laboratory following a shared protocol. It was not possible to prepare all the TMMs in the same laboratory, as the material could not withstand transportation without alteration of its properties. The calculation of TET is very sensitive to changes in the maximum measured temperature, and this is in turn depends on the thermal and physical properties of the TMM and the thermal stability during the experiment. An imperfect execution of the procedure of TMM preparation might have led to significant differences in the parameters that have an influence on ultrasound energy absorption. This exponential dependence on temperature is a fundamental weakness of using TET as a quantity for comparing exposures or treatments.



3.1.6 Conclusion

A framework for exposure and dose has been developed and published. The main dose quantities defined were related to thermal effects and were a) the instantaneous quantity "absorbed ultrasound dose rate" (the rate per unit mass at which energy is deposited by absorption of the acoustic wave in a specified medium) and b) the cumulative quantity "absorbed ultrasound dose" (the energy per unit mass which is deposited within a specified time by absorption of the acoustic wave in a specified medium). Gaining consensus and establishing an internationally accepted metrological infrastructure, including a dose concept for therapeutic ultrasound, which supports both engineering and clinical purposes will take time and require substantial further work involving NMIs, regulatory bodies, academic researchers, manufacturers and clinicians. The outcome of this will feed into the International Electrotechnical Commission standards and also into more easily accessible professional and technical good practice guidelines.

Absorbed ultrasound dose rate can be measured in reference materials calorimetrically with lower uncertainty (5%) than can be obtained by deriving temporal-average intensity from hydrophone measurements (12-15%) and thermal sensors can be lower cost and more robust than hydrophones. Together these advantages should encourage more reliable treatment planning.

The intercomparison of methods has shown that not all definitions of dose are easy to implement and can provide a good basis for standardisation. TET (also called thermal dose) is not a suitable quantity for a future Key Comparison because it is exponentially dependent on temperature rise. Measurement of quantities based on delivered ultrasonic energy, on the other hand, can be readily achieved.

3.2 Phantoms and measurement techniques for testing of dose concepts

3.2.1 Introduction

Work carried out under this objective was important for developing the measurement methods and materials which will be essential to establish traceability for exposure and dose quantities. The work has addressed the development of therapeutic ultrasound reference sources (3.2.2), the realisation and thermophysical characterisation of standard tissue mimicking materials (3.2.3 and 3.2.4), and measurement methods related to thermal mechanisms and to cavitation (3.2.5 to 3.2.8). Twenty related papers have been published.

3.2.2 Therapeutic Ultrasound Reference Sources

Stable operating conditions are essential for the reliable and reproducible characterisation of ultrasound sources. For many therapeutic ultrasound applications, this is a difficult task, since the required high electric input power may heat the ultrasound transducer during operation and thus change its electrical properties.

A particular scenario in which this leads to problems is secondary calibrations (e.g. of acoustic power meters or hydrophones), in which measurements obtained by the device to be calibrated are compared with measurements obtained by a calibrated device, which of course requires the same conditions for both measurements. A second example is bioeffect studies in which biological effects in tissue are correlated with acoustic field values. For this purpose, usually the acoustic value of interest (e.g. the peak negative pressure or the temporal average intensity) is measured in a first step and, in a second step, the biological effect after sonicating the tissue under the same conditions is evaluated. One task of the project thus was to develop stable reference sources and to investigate their stability both on a long term view (i.e. do the properties of the sources change over weeks or months) and on a short term view (i.e. does the output field of the sources change during applications that last some seconds).

Two therapeutic ultrasound transducers were chosen - one extracorporeal single element HITU transducer and one in-house made physiotherapy-like lithium niobate transducer. For the signal creation, a designated function generator and an rf amplifier were used. All devices were chosen based on previous experiences and on preliminary measurements concerning the stability and were integrated in a mobile rack. Since the stability of the output of the sources significantly depends on the stability of the input voltage, the latter was improved via two different complementary approaches:

In order to improve the relative stability of the input voltage (i.e. to reduce effects due to heating of the electronics), a feedback algorithm was implemented at PTB, which is based on continuous measurements of



the input voltage at the transducer and a respective recalculation and setting of the output voltage of the function generator, using a simple proportional control with adjustable control gain.

In addition, the absolute input voltage was stabilized with a calibration strategy of the voltage measurement facilities, which is based on internal calibration options of the used electronics as well as on a comparison of voltage measurements under the respective conditions (frequency, voltage range) with a DC calibrator and thermal voltage converters.



period. The variation was reduced from 1.5 % without feedback control to 0.7 % with feedback control.

To test the improvement of the input voltage stability due to the feedback control, the input voltage was monitored for a 60 s continuous wave (cw) sonication with and without feedback control. In order to prove the direct relevance for acoustic field values, the rms end-of-cable voltage of a membrane hydrophone was monitored simultaneously. The stability of both the input voltage and of the hydrophone voltage (i.e. of the acoustic field) is clearly improved (see Figure 5). Although the improvement is admittedly small in this case, it is likely to become more significant at higher voltages, which was not tested to avoid damaging the hydrophone.

Table 1 summarises studies to quantify the improvement that feedback brings in the stability of the transducer input voltage, indicating a lowering by a factor of approximately 6.

Table 1: Estimation of the uncertainty contributions "reproducibility" and "repeatability" of the input voltage with and without the feedback control. "Reproducibility" is estimated from the variations of the amplifier gain that was investigated bimonthly over a period of one year. "Repeatability" is assessed from individual measurements sets (short-term). Additionally, an uncertainty contribution for the absolute measurement of input voltage is estimated from experience for standard oscilloscope calibrations (3 %) and for calibrations against thermal voltage converters ("TVC", 0.3 %).

		WITH Feedback		WITHOUT Feedback	
А	reproducibility	0.3 %		3.0 %	
В	repeatability	0.4 %		1.1 %	
	Pythagorean sum (A ² +B ²) ^{0.5}	0.5 %		3.2 %	
		TVC	Standard	TVC	Standard
		Calibration	Calibration	Calibration	Calibration
С	Absolute measurement	0.3 %	3.0 %	0.3 %	3.0 %
	Pythagorean sum (A ² +B ² +C ^{2)0.5}	0.6 %	3.0 %	3.2 %	4.4 %

Furthermore, the long term stability of the output parameters (i.e. acoustic output power, peak compressional and rarefactional pressure as well as the pulse-pressure-squared integral) was tested at power levels up to 40 W by bimonthly measurements at PTB over one year. The measurement results show a satisfactory stability – they vary within ± 5 %. The variation is even smaller for all power measurements (± 2 %, which is on the



order of typical random variations). The remaining variations are assumed to be mainly due to positioning uncertainties and temperature variations during the hydrophone measurements.

3.2.3 Realisation of standard tissue mimicking materials

To develop measurement techniques, validate theoretical models and characterise specific HIFU ablation devices, tissue-mimicking phantoms with acoustical and thermal properties equivalent to human tissues are necessary. Although over a number of years many types of polymeric tissue have been proposed, the realisation of a tissue mimicking material (TMM) with reproducible and stable properties in terms of speed of sound, Young's modulus and attenuation coefficient still remain a challenge, which was the aim of this work.

Collaboration between INRIM, PTB and NPL has identified two different types of TMMs with different properties. INRIM has investigated two types of polysaccharides, Agar and Gellan Gum, as possible different materials to be used as the basis for the realisation of a TMM sample. Agar is a well-known polysaccharide, extensively used for the realization of TMMs. Agar has been largely studied from a mechanical and thermal point of view and its acoustic and mechanical properties can be altered for tuning to human tissues properties. Gellan Gum is a more complex polysaccharide. Over the last five years, this product have received more attention because of its temperature stability, higher mechanical strength and better clarity than Agar, besides a substantially lower cost, which makes it an attractive polymer for the realization of TMM matrix.

In particular, two different approaches have been followed in order to have reproducible mechanical and acoustic properties: i) one based on the homogeneous distribution of solid particles into the TMM and ii) the other devoted to the realization of a transparent attenuating TMM in order to reach similar values of human organs while maintaining an optical transparency to visualize the HIFU lesion. An extensive study on the polymerization mechanism of Gellan Gum has resulted in a simple preparation method to disperse solid particles (in our case silicon carbide and kieselguhr, a natural siliceous sedimentary powder), into the polymer matrix. Since it gels at higher temperature than agar, this prevents the settling of the particles and provides a TMM with homogeneous acoustic and mechanical properties.



Figure 6. Attenuation coefficient of 0.4M zinc acetate as a simple solution (green squares) and made into a gel with agar (2% by weight).

The second approach focused on the realization of a transparent attenuating TMM. Since solid particles obviously cannot be used for this purpose due to optical scattering, the main difficulty was linked to the identification of a substance that provides an adequate ultrasound attenuation. To do that, a study on ultrasonic absorption given by aqueous salts solutions has been carried out. Some hypothesis have been proposed to explain the ultrasonic absorption given by inorganic salts in general and also for zinc acetate, but for lower concentrations with respect to those ones reported for this scope. The origin of ultrasonic attenuation concerns the interaction (absorption-relaxation) between the ultrasonic waves and the equilibrium reactions of zinc ions, or undissociated salt, with water molecules. The volume variation related to the formation of these coordination complex is influenced by the pressure variation, and consequently volume, caused by ultrasonic wave. The measurement of ultrasonic absorption was extensively used in the '50s and '60s to study molecular interactions in pure liquids, binary liquid mixtures and ionic interactions in single and mixed salt

solutions. However, early studies concerning the application of this technique to aqueous solutions of inorganic salts have been largely disregarded. Several trials have been carried out at INRIM, finally concluding that zinc acetate [Zn(CH₃COOH)₂] is the best choice for our scope. It has no particular toxicity, it is not paramagnetic, so that TMM prepared with this salt can also be used in NMR equipped HIFU apparatus, and, finally, it shows an adequate absorption in the frequency range of interest (1-10 MHz) as function of salt concentration; in particular concentrations around 88 g/l (0.4 molar) have proved to be appropriate. This can be used as a simple solution to provide an attenuating fluid with density 1.044 g/cm³, or made into a solid gel. The attenuation



coefficient at this concentration is approximately 0.65 dB/cm^{1.5} (see Figure 6 above) and the speed of sound was aproximately 1500 m/s as a liquid and 1511 m/s as a gel. In addition, both polysaccharide matrix Agar and Gellan Gum have been tested. Unfortunately, concentrated solutions of Agar (>1%) produce opaque gels, so that Gellan Gum has been found to be the more suitable matrix if greater optical transparency is required. An alternative, which may be useful in some cases, is to dissolve polyethylene glycol in the zinc acetate solution to increase the viscosity without gelling and maintaining transparency. The use of zinc acetate gives the possibility to realize a tunable TMM, simply by varying salt concentration.

3.2.4 Traceable thermophysical characterisation of tissue mimicking materials

For the determination of thermal properties of the tissue mimicking materials, it has been chosen to try to adapt state of the art instrumentation to measure the specific heat capacity and the thermal diffusivity of selected materials. At first, a prototype of a modulated adiabatic calorimeter has been considered because of its high accuracy and precision (<0.5%). Measurement cells have been redesigned and adapted to host injected liquid that should solidify into a gel inside the cell. However, due to the high viscosity and surface tensions of samples, it has been necessary to increase the cell inner diameter up to 2.5 mm. Although it has been possible to fill the cell, this operation was difficult and strongly influenced the repeatability of the measurement (5%) so that only a few samples were measured using the modulated adiabatic calorimeter. On the other hand, a modulated differential scanning calorimeter (mDSC) showed better performance allowing results to be obtained with a typical uncertainty of the 2% (including repeatability) in the temperature range of (10 and 80) °C.

Although DSCs usually allow uncertainties in the order of 5-10% to be obtained, it has been possible to improve the performance of the instrument by refining its calibration procedure. Firstly, a standard DSC calibration has been carried out only considering a limited temperature range. Cell calibration is necessary to account for the residual heat flux between the two furnaces that should not be present in the case of an ideal cell. Therefore, after heating and cooling the furnaces with and without reference materials (NIST certified sapphires), it has been possible to calculate cell parameters and the resulting baseline, representing heat flux between furnaces, which can be considered to be constant with negligible deviations from the zero value. At the end of this standard calibration procedure the instrument was ready to carry out heat flux measurements. However, specific heat capacity cannot be measured with the desired uncertainty of 1%. For this reason, it has been necessary to proceed with a further calibration step allowing to improve the accuracy of specific heat capacity measurement. This step was completed by measuring the specific heat capacity of additional NIST certified sapphires with masses of approximately 25 mg (much smaller than those used for heat flux calibration). This procedure permits more accurate determination of the correction factor which is used for calculating the specific heat of the sample.

During preliminary tests, it has been tried to solidify gel directly into DSC pans without succeeding, because the sample tended to stay on pan walls instead of on its base. So it was decided to prepare large samples and then extract few milligrams for the measurements. A drawback of this procedure is that it is necessary to cut off a slice of gel and not a pellet, however the slices were dropped into the bottom of the pan and moved around, helping the specimen to adhere to the pan flat surface. This empirical procedure improved measurement repeatability to the level of 1%.

The measurement procedure was programmed according to a scheme called *heating-cooling-heating*, that plans to first equilibrate the sample at a lower temperature and then heat it to the maximum temperature at a rate of 10 °C/min: this preliminary heating allows non-homogeneous molecular bonds generated after the solidification of the gel to relax. Next, a temperature ramp is applied from the higher to the lower temperature to determine absolute heat capacity. Finally, the ramp is reversed, heating the sample again. These last two runs provided specific heat capacity values with an agreement better than 0.5%. In this frame, specific heat capacity is determined as the average of the results obtained using samples of different weight.

The uncertainty associated with the heat capacity measurements could be estimated considering contributions of different sources evidenced during calibration procedure. To be rigorous, uncertainty introduced by temperature measurements should also be included. However, this contribution is negligible with respect to other sources of uncertainties because specific heat capacity is only weakly dependent on temperature (see Figure 7). Table 2 reports the major sources of uncertainty and their size with a coverage factor k=2.



Uncertainty type	Contribution	Source		
Absolute heat capacity calibration	<0.5%	Reference material and calibration constant		
Measurement repeatability	<1.0%	Including thermal contact		
Repeatability	1.0%	Material preparation		
Mass	<1.0%	Sample weight measurement		
Overall	<2.0%	Quadrature sum		

Table 2. Expanded uncertainty budget (k=2) for specific heat capacity measurement.



Among seven different materials considered, the most promising specimens were shown to be Gellan Gum $2\% + Zn(CH_3COOH)_2$ and Carrageenan $2\% + Zn(CH_3COOH)_2$ because of their thermal stability (absence of phase transitions in the considered temperature range) and because their specific heat capacity values are closer to those of real tissues like liver (3540 J/(kg °C)). Unfortunately Carrageenan has shown a too limited mechanical stability. Figure 7 shows the measured specific heat capacity for the most promising samples. Agar $2\% + Zn(CH_3COOH)_2$ sample did not show the required stability in term of thermal properties: when heated and cooled it showed negative heat capacity peaks revealing melting of some components. Further investigations are needed for this specimen.

3.2.5 Measurement Methods - Ultrasound Thermometry

Reliable temperature measurements *in situ* (i.e. in tissue or in tissue-mimicking materials) are a prerequisite for any investigation on i) both the relationship between (acoustic) exposure quantities and (thermal) dosimetric quantities and ii) the relationship between dosimetric quantities and effect quantities (i.e. so called bio-response studies). One of the possibilities to measure temperature *in situ*, besides the (invasive) usage of thermocouples and the (expensive) usage of magnetic resonance imaging (MRI), is ultrasound (US) thermometry. One task within the project thus was to accomplish an US thermometry setup at PTB with a standard diagnostic ultrasound device and to investigate its suitability for *in situ* temperature measurements from a metrological point of view. In collaboration with HoMe and CSIC it was also evaluated whether the results could be confirmed using a different diagnostic US device in a different lab and, in the case of CSIC, different tissue-mimicking materials. HoMe further evaluated the influence of different ways of data analysis on the final measurement uncertainty.



The temperature-change estimation method studied within the project is based on the thermal dependence of the ultrasound echo that accounts for two different physical phenomena: local change in speed of sound due to changes in temperature and thermal expansion of the propagating medium. The former produces an apparent shift in scatterer location, and the latter leads to a physical shift. The two effects together lead to echo time-shifts that can be estimated and can be related to local changes in temperature in the propagating medium.

Within the project, a standard commercial diagnostic ultrasound scanner (ESAOTE Biomedica Deutschland GmbH, Hallbergmoos, Germany) was used at PTB. It was solely modified by the manufacturer to provide access to RF data to a separate computer connected via an optical link. A diagnostic probe with a centre frequency of 10 MHz and sampling frequency of 50 MHz was chosen to maximize the signal to noise ratio (SNR) of the RFdata from the different imaging targets. The time shifts δt were calculated from the recorded rf signals at all points using a cross-correlation method in Matlab. Cross-correlation processing was done with 25% overlapping windows around 6 λ each (λ is a wavelength of the diagnostic ultrasound). It defines the spatial resolution of the method as 0.34 mm for the employed ultrasonic probe. After the calculation, the time shifts $\delta t(z)$ were filtered along axial distance z with a three-point median filter. This filter removed any spikes that might be present in the displacement data. Moreover, in order to reduce small spatial ripples usually present in the time-shifts δt estimates, a sigmoid function fit was used. This step was necessary since small errors in the displacement estimate lead to large errors in its derivative. Finally, the result was differentiated along the axial direction and scaled by $kc_0/2$ to obtain the temperaturechange map estimates $\delta T(z)$. Here, k is a materialdependent proportionality constant comprising the thermal expansion and the temperature-dependence of the speed of sound c_0 that has to be obtained by calibration measurements in advance. Two phantom materials were tested: one was a gelatine-based



Figure 8. Photograph of the setup at PTB for US thermometry. The therapeutic US transducer (right) sonicates into and heats the tissue-mimicking material (black). The diagnostic imaging probe (top) is used to measure the temperature.



Figure 9. Temperatures estimated on the basis of the echo shift method (points) and simulated (solid line) at the focus of the HIFU source for different input voltages in the agarbased gel: black: $39 \vee (3 \text{ W})$, red: $58 \vee (7 \text{ W})$, blue: $65 \vee$ (8 W), magenta: $97 \vee (16 \text{ W})$.

material made according to the recipe in IEC60601-2-37; the other (shown in Figure 8) was an agar based gel containing (in 1 litre) water (850 ml), agar powder (25.5 g), N-propanol (127.5 ml) and graphite powder (10 g). The measurements were further compared at PTB with thermocouple measurements and results obtained from numerical modeling using the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation to model the acoustic field and Pennes' bioheat equation to model the resulting temperatures. The comparison of the simulated and measured results shows good agreement. The largest and somewhat systematic differences were observed in the cooling phase as it was also for the temperatures measured with thermocouples. This was found to be due to the employed fitting functions that strictly are appropriate for the heating time and for the frame-to-base analysis only (see Figure 9).

In order to obtain another independent validation, a similar setup was accomplished at HoMe, using a different diagnostic US device (SonixTOUCH ultrasound imaging system, Analogic Corp.). The results from PTB and



HoMe generally showed good agreement. Furthermore, a detailed study was performed at HoMe on the influence of different ways of data analysis on the results and their uncertainties:

Method 1a - Frame-to-frame method: Cumulative time-shifts were calculated from each frame to the previous one.

Method 1b - Frame-to-base method: Cumulative time-shifts were calculated from each frame to the base frame (i.e. the one recorded before heating).

Generally, method (1a) was found to be more stable against both mechanical and signal changes. The second method (1b) however proved to be more accurate since uncertainties do not add up over time. The frame-to-frame method can be thus used for a rough estimation of the location of the focus zone and to some extent for estimating the size of the focus. However it has major shortcomings, so that it is not suitable for accurate laboratory temperature calculation. Detected cumulative time-shifts are very small leading to huge uncertainties of the calculated temperatures. These uncertainties add up from frame to frame. Only few scanlines can be used for temperature calculation. The frame-to-base methods produced good results in total temperatures, temperature curves over time and spatial distribution. As far as comparable they agreed with thermocouple measurement. The best results and the smallest uncertainties (less than 11% in the focus zone) were obtained using the continuous frame-to-base algorithm with two-dimensional cross-correlation. Accuracy can however be further enhanced significantly by improving filtering algorithms and interpolation of sampled diagnostic ultrasound data.

A further independent validation was made at CSIC using another modified diagnostic US device (Philips sono Diagnost 360) and phantoms produced by NPL. Though promising, especially for low temperature increases, the results were not as good as for PTB and HoMe due to difficulties encountered when determining the thermo-acoustic properties of the phantoms.

3.2.6 Measurement Methods - Cavitation measurements

Although the project was mostly focused on quantities related to thermal effects, there are several other mechanisms relevant to biological interaction of ultrasound. In particular, cavitation was picked out as being an area of interest within the user community. Concerning the quantification of cavitation, there exist neither clear definitions of quantities (e.g. "cavitation threshold" or "cavitation onset") nor standardized ways to measure cavitation or cavitation probability. Available literature data are often hard to compare due to the different employed methods, materials, signal types, etc. Within the project, a simple echo-reflection method based on the measurement of backscattered signals from cavitation bubbles was developed initially at NPL and then further developed at PTB, which might help to fill the mentioned gaps in cavitation quantification.

The method is based on the measurement of voltage signals from reflected ultrasound waves: the ultrasound signal is focused into the material to be investigated, where a small amount of the ultrasound signal is reflected due to small inhomogeneities or scattering particles. When cavitation occurs, a cavitation bubble forms and the reflected signal is significantly higher due to the impedance mismatch at the bubble interface. Since the employed HIFU transducer as any electroacoustic transducer is capable of transforming the received ultrasound signals in voltage signals, the latter can easily be used to monitor the occurrence of cavitation events. A setup was accomplished at PTB for automated measurements, including a software with a user friendly graphical user interface that was made available to the project partners.

Furthermore, a criterion was defined at PTB, based on the previously recorded voltage signals and their standard deviation to distinguish between negative events (i.e. no cavitation occurrence) and positive events (i.e. cavitation occurrence) or unclear events on a quantitative and objective basis (see Figure 10). The criterion proved to be stable for all considered cases and for different types of signals and might be beneficial on finding a standardized way for cavitation detection.

All obtained (empirical) cavitation probabilities (i.e. the ratio of positive events to all clear events) could be adequately described with a Gaussian cumulative distribution function of the focal peak rarefactional pressure yielding the expectation μ and the standard deviation σ for every experiment. The dependence of μ and σ on the type of signal (i.e. burst length, pulse repetition time or duration of the signal) was studied systematically for tissue-mimicking materials made of Agar and water (see Figure 11).





PTB shared the underlying algorithms and software with HoMe and CSIC, where similar measurements shall be performed beyond the end of the project.



3.2.7 Measurement Methods - MR thermometry

MRI based quantification of temperature change can be achieved by assessment of multiple parameters. While changes in T1 or T2 relaxation times show good correlation with temperature changes. the measurement of these parameters does not fulfill the requirements for temporal resolution. A reliable technique for determining temperature change in relation to a baseline image is the proton resonance frequency shift (PRFS), which shows a linear relationship between temperature and the tissue's resonance frequency for a certain temperature range. Fast image acquisition techniques using echo planar imaging (EPI) are available to achieve high temporal resolution. Initial experiments have been executed with a modified gradient echo sequence to evaluate the feasibility of the method before switching to a PRFS sequence with EPI readout. Two different HIFU setups have been used to perform the experiments: a) a 256-channel phased array transducer (0.5-1.5 MHz, Imasonic/IGT, France) and b) a custom built fixedfocus transducer (1.7 MHz). For the latter, the freefield parameters were measured by PTB. This data has been used for inverse validation of the experimental results using software simulation.





Different types of gel phantoms have been used for the experiments, among them those proposed by INRIM (agar + zinc acetate) and some that could be manufactured in-house (gelatin/agar + evaporated milk). After eliminating uncertainties concerning phantom manufacturing it is possible to reliably obtain reproducible results (+/- 1°C) in consecutive sonications with identical parameters (see Figure 12). Acquisition times of approximately 100 ms per slice with a spatial resolution of $1.1 \times 1.1 \times 2.5$ mm could be obtained by FhG without any significant impact on image quality. With sufficient temporal and spatial resolution and minimization of partial volume effects by proper slice alignment MR thermometry proves to be a suitable choice for thermal dose quantification. Furthermore it could be shown that numerical calculation by using the HIFU setup's free-field parameters and phantom properties as input for HIFU simulation methods resulted in comparable temperature values to experimental results.

FhG and PTB collaborated to evaluate the MR compatibility of thermochromic liquid crystal (TLC) thermometry and then to perform a temperature measurement using the TLC foils synchronously with MR thermometry. In addition, FhG with INRIM and PTB have shown that the improved ultrasound tissue mimics also mimic human magnetic resonance properties, specifically relaxation times.

3.2.8 MR assessment of non-thermal effects

3.2.8.1 MR acoustic radiation force imaging

MR acoustic radiation force imaging (MR-ARFI) is a non-invasive quantitative MR-method to assess the radiation force induced tissue displacement due to a travelling ultrasound wave. Similar to MR diffusion imaging, MR-ARFI exploits the properties of bipolar gradients for motion encoding to capture the local displacement that occurs due to ARF in the focal spot. Apart from the strength of the HIFU burst, the observed displacement (within the range of micrometers) depends on the elastic properties and absorption capabilities of the tissue or phantom and can be directly related to the effective force induced by the ultrasonic waves.

A custom built MRI pulse sequence employing such bipolar gradient pairs has been implemented in the course of this project to enable acquisition of ARF images on the available MR hardware. The sequence also provides functionality to send trigger signals to external devices. This is necessary to trigger the HIFU pulses in synchronicity with the pulse sequence. Measurements with three different gel phantoms (agar + milk, gelatin + evaporated milk, agar + zinc acetate) have been executed. As the moment of maximum displacement



depends on HIFU intensity, frequency and gel properties, it is necessary to capture a time series with varying ultrasound pulse offsets in relation to the motion encoding gradients. For each gel 8 to 11 image samples have been acquired to reflect the evolution of the displacement depending on the HIFU offset time (see Figure 13).

To correlate the experimental results to a pressure simulation using the free-field parameters of the transducer, it is necessary to densely sample the spatial extent of the ultrasonic field with MR-ARFI, which is suggested as future work.



3.2.8.2 MR based cavitation detection

Aside from heating, acoustic cavitation is a second major ultrasound effect with significant biological relevance. Occurrence and dynamics of cavitation bubbles in tissue is a rather complex process. For this reason a reliable detection and quantification of cavitation is important for the definition of an ultrasound dose. MR imaging bears potential to non-invasively detect cavitation as the occurrence of microscopic bubbles has explicit effects on the magnetic properties of the tissue being evaluated by changing the magnetic susceptibility. A technique that is routinely used in neuro imaging is to detect changes in T2* decay due to higher oxygenated blood and thus identifying activated brain regions during such experiments. It is assumed that a similar effect of spindephasing should be visible during the occurrence of cavitation, as the presence of microscopic gas bubbles will have an effect on the T2* decay. Such measurements are executed by sampling the T2* decay curve and performing an exponential fit to the samples. As purposely inducing cavitation requires high ultrasound intensity and short exposition times (low duty cycle) to prevent heating, it is necessary to minimize MR acquisition time. For this reason a fast multi-contrast EPI sequence has been developed and tested by FhG on two different gel phantoms (gelatin + evaporated milk, agar + evaporated milk). Comparison of the images with activated HIFU (20 ms pulses) to the reference images without ultrasound indeed revealed a subtle decrease in T2* (see Figure 14 above). However it is not yet definitely confirmed that the decrease is exclusively caused by cavitation bubbles or bubble clouds only. For future work a passive cavitation detector method or an echo-reflection method should be used to confirm the evidence of cavitation.

3.2.9 Conclusion

The therapeutic ultrasound reference sources setup developed within the project shows a satisfactory shortand long-time stability. This implies, on the one hand, that the used devices seem to be appropriate for calibration setups and, on the other hand that the feedback algorithm and the calibration strategy seem to be appropriate approaches towards an improved stability. In addition, the estimation of uncertainties for the input voltage yields a reduction by a factor of 6. The presented setup may significantly improve the predictability of field values in exposimetry and bioeffect studies, as well as reduce the uncertainties of secondary calibration



of any device in therapeutic ultrasound fields. One additional point is that, with the presented setup, interlaboratory (Key) comparisons could become feasible, where true acoustic values (power, pressure, intensity,...) are compared instead of, for example, radiation conductance values.

Stable and reproducible reference materials will be essential in providing traceable measurements for dose and exposure. A new approach for the realization of tissue mimicking materials has been found. The attenuation of the ultrasonic field is given by the solutions of organic salts: specimens have been produced which exhibit adjustable acoustic absorption coefficient, and density (comparable with different human tissues) and allow transparent and homogeneous TMM with tuneable acoustic and mechanical properties which can be made reproducibly and are suitable for therapeutic ultrasound. The development of zinc acetate gels provides a route to much reduced variability and lower uncertainty in future. The experience in the realisation of this type of TMM will result in more defined processes for the realisation of more stable and repeatable materials for dose measurement and for other uses including QA testing and transfer standards.

Knowledge of the specific heat capacity and the thermal conductivity is also an important consideration because these are essential for describing heat diffusion phenomena and determining the behaviour of ultrasound-induced temperature transients. In this case a new method, involving mDSC, has been proposed and obtained results are in agreement with those measured with classical hot-plate methodology. Considering that mDSC allows samples smaller than 25 mg to be measured, it is possible to characterise reference materials in a non-destructive way.

For non-invasive, ultrasound based temperature measurement, experimental results generally show the feasibility of the echo-shift method for estimating the temperatures in two dimensions in a tissue-mimicking phantom. Time-shift estimation of backscattered echo signals constitutes a relatively simple method to follow temperature changes. The availability of a reference signal and control of (initial) temperature, combined with the consistency of an empirical linear relation between echo-shift and temperature, strongly suggests that a calibrated temperature measuring system is possible with this technique. Especially the echo time-shift method using a continuous frame-to-base algorithm with two-dimensional cross-correlation can be a cheap, comparatively accurate and fast method for estimating temperature changes in a phantom. Therefore it might be at least a good option for fast quality control of therapeutic ultrasound devices in clinics before treatment and could be used for laboratory dosimetry.

Using MR-thermometry (which is appropriate for MR-guided HIFU systems) and minimizing partial volume effects by proper slice alignment, it has been shown that it is possible to achieve sufficient temporal and spatial resolution to show that MR thermometry is a suitable choice for thermal dose quantification. Furthermore it could be shown that numerical calculation by using the HIFU setup's free-field parameters and phantom properties as input for HIFU simulation methods resulted in comparable temperature values to experimental results

The ultrasonic echo-reflection method developed in this project to detect and quantify cavitation proved to be suitable for all investigated types of ultrasound signals. It is easy to implement and to use, benefits from inherent alignment of the sending and the receiving geometries due to the transducer's focusing geometry and it is not restricted to transparent materials (like optical methods). It might help finding standardized ways of cavitation detection and standardized definitions of cavitation quantities. Due to the promising results, measurements in different materials and for different sonication conditions are continuing after the end of the project, working towards improving the empirical predictability of cavitation based on known quantities and material quantities to be obtained.

MRI based methods for detecting cavitation in phantoms revealed a subtle decrease in T2* by comparing images with cavitation to reference images without ultrasound. However it is not yet definitely confirmed that the decrease is exclusively caused by cavitation bubbles or bubble clouds only. The method to detect changes due to radiation force also shows promise. To correlate the experimental results to a pressure simulation using the free-field parameters of the transducer, it is necessary to densely sample the spatial extent of the ultrasonic field with MR-ARFI, which was left as future work.



3.3 Methods for the assessment of commercial machines and comparison of treatment effects and efficiency

3.3.1 Introduction

Work carried out under this objective was important to support the testing of clinical therapeutic ultrasound (commercial) systems. The work has addressed the development and evaluation of two prototype traceable transfer standards (infrared imaging - 3.3.2 - and thermochromic liquid crystal - 3.3.3) which were potentially suitable for comparing treatment delivery systems. Six related papers have been published.

3.3.2 Infrared imaging transfer standard

In the last decade, the use of Focused Ultrasound Surgery (FUS) for therapy has grown substantially. Most of HIFU transducers are inextricably embedded in the clinical device and there is a growing need for fast, reliable and accurate quality assurance (QA) strategies. The use of multi-element transducer arrays generates a vast range of configurations that could be tested. In radiotherapy, photographic film has been used to map the spatial distribution of energy incident on a specific plane since the '50s and, more recently, EPIDs (electronic portal imaging devices) have been developed which record the energy distribution digitally (for instance using amorphous silicon detector) instead of on film.

The use of thermal imaging acquired by infrared (IR) cameras has been developed at NPL in collaboration with MSU for fast and quantitative measurement of high power acoustic fields because of its combination of speed of data acquisition, its spatial resolution and its wide dynamic range of temperature. As part of this project we have developed a prototype traceable transfer standard showing that the heating pattern closely follows the free-field intensity distribution despite the presence of a totally reflecting air interface.



Figure 15. Left: Rotated diagram of the IR measuring system showing the camera in its housing pushed against the TMM target; the HIFU transducer separated from the TMM target by approximately 10 cm of coupling fluid. Right: The system in position on the MR bed: the HIFU transducer is underneath the bed.

The IR camera used was a PI-200 (Optris Infrared Thermometers, Berlin, DE). It is compact (46 x 56 x 90 mm), powered from a computer USB port and has. 120x160 pixel resolution and a maximum frame rate of 128 Hz. It was set to operate over the temperature range -20 °C to 100 °C. In normal use, temperature data can be exported with a resolution of 0.1 °C but this has been improved by extracting data from the proprietary raw video file and processing them independently, improving the resolution up to 0.02 °C. The camera is mounted within a waterproof housing (Figure 15). On the front surface a 6 µm Mylar membrane functioning as the measurement surface; the acoustic window has a diameter of 100 mm. The distance of the camera from the acoustic window is adjustable providing spatial resolution from 0.05 mm to 0.4 mm per pixel and a field of view of 8x6 mm to 60x45 mm, respectively. A 10 m USB cable with a built-in amplification chipset (BlueRigger Active Extension, Redmond, WA, USA), is sealed into the base. A 65 mm high cylinder of TMM was

used as the target region: the length of the TMM was chosen so that the near and the far field of the acoustic beam under investigation could be tested. The TMM was an agar-based gel made at NPL which followed the formulation given in IEC60601-2-37. The main acoustic properties of the TMM are an attenuation coefficient which is almost linear with frequency (0.49 ± 0.05 dB/cm/MHz), a speed of sound around 1540 ± 8.7 m/s, density of 1070 ± 30 kg/m3 and specific heat capacity of 3770 ± 3% J/kg/K.

Tests on a clinical system were performed by ICR on a Sonalleve MRgFUS system (Philips, Vantaa, Finland) at a distance of ~1 m from the edge of the magnet bore of a 3.0 T Philips Achieva MRI scanner (i.e. the Sonalleve patient bed was in its 'pulled-out' position): this is also shown in Figure 15). This bed has a plastic membrane which seals the oil coupling chamber in which the transducer is mounted on a 5 degree of freedom positioning system transducer. The transducer is a 256 element array, with a geometric focal length of 14 cm



and a diameter of 14 cm; the system can be operated at 1.2 or 1.45 MHz. The transducer was driven in continuous mode at 1.2 MHz for 3 s. Thermal image sequences were saved at a frame rate of 20 Hz.





The system was usable inside the MR room with low thermal noise levels and enabled to obtain maps of the energy distribution (see Figure 16) in the selected measurement plane (hence potentially revealing information about degradation in the focusing capabilities of the system) and also provided estimates of the actual intensity values. Measured rates of temperature increase ranged from 0.1 °C/s to 34 °C/s, correspond to I_{spta} values of 2.1 W/cm² and 724 W/cm² respectively. The main problem encountered was that, at higher output powers, the images were affected by what seems most likely to be separation between the acoustic window and the tissue mimicking gel which forms the target region: this separation is most likely caused by radiation forces on the window. This should be addressed in future versions by using a solid (rather than gel) target material.

3.3.3 Thermochromic liquid crystal transfer standard

Several acoustic exposure quantities or dosimetric quantities can be measured satisfactorily in laboratory environments. However, most of the respective measurement approaches are not suitable for clinical environments, where measurements have to be fast to avoid or reduce down times of the devices and easy to perform/analyze by the clinical staff. Therefore, a transfer standard was developed at PTB aiming at fast and easy transient measurements of temperature in 2-D during the application of therapeutic ultrasound that can be calibrated against traceable measurement methods. In collaboration with FhG, the MR compatibility of the setup was assured and first tests in a clinical environment were performed.

The setup shown in Figures 17 and 18 is based on the temperature-dependent color of thermotropic liquid crystal (TLC) foils. Those foils were integrated in newly developed TMM and a mechanical setup was accomplished which allows monitoring the color of the TLC foils with a camera during the sonication. Several issues had to be covered during the development of the setup, like the reproducible illumination of the TLC foils, as well as the necessity to protect the camera against the sound field and the magnetic field in case of application within MR scanners. The first issue was solved by the use of a diffuse illumination via a LED, a lightguide (LG) and a diffusing prism (P). The protection against ultrasound was assured by the use of strongly absorbing oil and indirect monitoring of the TLC foils via a totally reflecting surface (G). MR compatibility was assured by the usage of MR compatible materials without exception. The only piece that could not be realized with MR compatibility, the camera, is kept away from the inner bore of the MR scanner.

Traceable calibration of the assignment of colour to temperature was realized with an adjustable electrical heating foil, calibrated thermocouples and deep investigation of different ways of analyzing colors.

An appropriate software was accomplished by PTB that reads automatically taken pictures or videos from the digital camera, converts them into colour matrices and those into temperature matrices. It was found that analysis in HSV (hue, saturation, value) color space yields a better accuracy and reproducibility than in RGB (red, green, blue) color space.





Figure 17. Schematic principle of the TLC transfer standard.



Figure 18. Photograph of the TLC transfer standard during tests in the MR scanner at REG(FhG) in Bremen. The sectional drawing in Figure 17 corresponds to the black box left – the camera is positioned at the right end of the grey tube to be kept away from the static magnetic field of the MR scanner.

3.3.4 Conclusion

NPL has developed a prototype system for mapping of the energy deposition on the surface of a TMM in a single plane of a FUS (Focused Ultrasound Surgery) beam. The detector is an infrared camera which measures the temperature change on the surface of a tissue mimicking target region. This work shows promise as a future ultrasound equivalent to a radiotherapy EPID (Electronic portable imaging device). However, developments are required both in theoretical and experimental design to bring this approach to a metrological acceptance. From a theoretical point of view, further advances are required in the modeling of the effect of the air interface in thermal deposition and distribution, while new solutions have to be developed to reduce uncertainty factors and improve repeatability of the experiments, especially when high intensity fields (I_{spta}>100 W/cm²) are investigated.



Although the TLC-based transfer standard developed at PTB was found to be generally suitable to monitor transient temperature distributions in a plane, the tests in FhG showed also that the accuracy of the measurements is too low for the high level of complexity of the setup and the analysis of the measurements. Furthermore, the necessary usage of oil and other chemicals within the phantom and risk of leakage into the clinical devices was found to be critical. The full implementation tested has proved to be a too complicated for general use but simplifications of the principle will be further developed at PTB, NPL and ICR in the future.

3.4 Linear and non-linear ultrasound propagation through phantoms and anatomical structures

3.4.1 Introduction

Work carried out under this objective was important to support future treatment models and international safety standards. The work has addressed the development of an acoustic holography method (3.4.2), improved modelling of linear and nonlinear wave propagation in soft tissue in three dimensions (3.4.3), propagation in and around bone (3.4.4), and thermal interaction with soft tissue and bone (3.4.5). Ten related papers have been published.

3.4.2 Acoustic holography for the characterization of therapeutic sources and fields

Though some HIFU treatments have progressed to clinical use, challenges remain for ensuring its safety and efficacy. A key component of these challenges is the lack of standard approaches for accurately characterizing the acoustic pressures generated by clinical ultrasound sources under operating conditions. A method named acoustic holography was developed and successfully validated for characterizing 3D outputs of HIFU sources of various geometry including multi-element clinical arrays. This work was been carried out in collaboration between NPL, Moscow State University, University of Washington and Philips Healthcare.

Specific steps of the method are the following.

- 1. First, at a low output level, a calibrated hydrophone is used to measure in water the linear pressure magnitude and phase over a planar region in front of the source (see Figure 19). The position and orientation of such a region should be chosen so that it is crossed by most of the ultrasound field emitted by the source. A practical choice would be to position the measurement plane close to the source, with an orientation perpendicular to the ultrasound propagation direction and a size that extends beyond the geometrical cross section of the ultrasound beam. Such measurements represent a 2D hologram of the full 3D sound field.
- 2. Second, these measurements are used to holographically reconstruct the surface vibrations of the transducer and to set a boundary condition for a 3D acoustic propagation model.
- 3. Third, at a near-source location, the linear pressure magnitude is measured across a range of clinically relevant output levels, including the level used in holography measurements. The measurement location ideally should be near a local pressure maximum, while also being close to the source to minimize the possibility of nonlinear propagation effects. This single-point measurement allows relation of the source pressure level at various output settings to the source pressure level used for the hologram measurements.
- 4. Finally, nonlinear simulations of the acoustic field with a realistic boundary condition provided with the method are carried out over a range of source power levels. Simulation results can be validated for propagation in water by comparison with direct hydrophone measurements at the focus at both low and high power levels.



The acoustic holography approach utilizes linear field measurements to i) quantify the acoustic output level, ii) capture the pattern of vibrations at the transducer surface, and iii) define a realistic boundary condition of ultrasound source for a 3D nonlinear acoustic propagation model at any output settings of the source. In addition, the total acoustic power calculated from the measured hologram can be used to determine the source power at all measured output levels. At these low pressure output conditions, agreement between calculated and measured fields within approximately 2% for pressure magnitude could be achieved over a large part of the field.



Figure 19. A diagram illustrating acoustic holography method to fully capture the vibrational pattern of the ultrasound source and the 3D field it generates based on a 2D pressure scan in a plane close to the transducer (shown towards the left side).

3.4.3 Wave3D field modelling software

NPL collaborated with MSU. FDA and UCL in developing improved modeling capabilities. Two literature reviews were performed. The first reviewed the governing equations used to model high-intensity ultrasound fields, comparing the utility of the models and their applications. The second review investigated the range of numerical methods used to solve the governing equations, and the hardware requirements for each method. From these twin investigations a powerful shared memory high-performance computing system was purchased, and a modeling software, entitled Wave3D, was developed, which matched the governing equation, numerical method and hardware to produce a powerful, robust versatile solver.



commercial finite element package (red) and an angular spectrum calculation (blue).

from single element transducers as well as phased arrays.

Wave3D acquired can use experimentally holography data, or computed data as an input into a pseudo-spectral forward marching scheme (Figure 20). This means that it computes the time varying 3D acoustic field by taking one Fourier transform in time, and two spatial dimensions and calculating the acoustic field - for all times - at a plane, and then marches forward in space and computes the next plane. The code uses an operator splitting approach, which enables the differing physical phenomena of diffraction, attenuation and nonlinearity to be handled separately, thus allowing the most appropriate and accurate method for each phenomenon to be applied. The operator splitting approach was extended to be second-order accurate, using Strang splitting. Holography offers a robust input, which can be used to propagate fields

The acoustic solver provides output to the thermal solver which includes perfusion modelled by the Pennes' bioheat transfer equation, and also permits some discrete vessel structure. The coupling between the acoustic and thermal models includes contributions from shock-like enhanced heating, where the energy deposition depends on the height of the shock rather than the intensity. The calculation of the shock height has been related to the width of a fully developed shock. This enabled a way of specifying when an additional heating mechanism would contribute the thermal field, and enable validation against simple analytic solutions. The thermal field then can further be used to compute a dose field according to a cumulative equivalent minutes formulation.



Both the thermal field and the dose field can accept inhomogeneous domains, and indeed, the dose field has been designed to include differing treatment threshold levels for dose. Thus, if some tissue is more thermally sensitive and can be designated as treated if it is exposed to e.g. 120 cumulative equivalent minutes, rather than 240 cumulative equivalent minutes, this can be incorporated into computations of the delivered dose (Figure 21).

A new development was the application of thresholding algorithms to indicate the regions where the likelihood of cavitation exceeds a specified threshold (see Figure 22 below): at present the likelihood depends on the peak-negative pressure but other criteria could be incorporated.



3.4.4 Elastic wave modelling in bone

There are many applications of therapeutic ultrasound in which ultrasound waves interact with bone. These include HIFU therapies delivered through the ribs or skull, and low-intensity ultrasound therapies used in physiotherapy for the treatment of soft tissue and bone injuries. In both cases, the heating of bone and surrounding tissue needs to be controlled; either to avoid thermal damage, or to ensure an adequate treatment has been delivered. The accurate assessment of heating effects in bone and other dense connective tissue due to ultrasound waves is thus important, particularly in the development of metrological approaches to quantify thermal dose.

The understanding of bone heating in a clinical setting can be greatly advanced through accurate physical and numerical models. However, unlike ultrasound heating of soft tissue, the heating of bone is complicated by the presence of a fluid / solid interface. In this case, the generation, propagation, and absorption of shear waves within the bone must also be considered. The absorption in bone is considerably higher than in the surrounding soft tissue (roughly an order of magnitude), and the absorption of the shear wave is approximately twice that of the compressional wave. Accurately accounting for this will likely have a significant impact on the accuracy of models used to predict temperature rises in the region of bones.

To account for power law absorption, a macroscopic continuum-mechanics model including a phenomenological term was developed. This was based on a fractional Kelvin-Voigt model of viscoelasticity, where the fractional terms are written as spatial (rather than) temporal derivative operators. The model was derived by splitting the particle velocity into compressional and shear components using a dyadic wavenumber tensor. This allows arbitrary power law absorption parameters to be independently specified for the compressional and shear waves. The model was shown to exhibit two distinct modes of behaviour depending on the value of the spatial wavenumber relative to a high-wavenumber threshold.

An efficient software implementation of the fractional Kelvin-Voigt elastic model as well as a conventional Kelvin-Voigt model was developed in MATLAB within the framework of the open-source k-Wave toolbox. A



numerical example of using the fractional Kelvin-Voigt model is shown in Figure 23. This illustrates the transmission of ultrasound from a focused transducer through the human skull. The simulation was performed using a grid size of 576×768 grid points, a grid point spacing of $167 \mu m$, a time step of 11.25 ns, and a total simulation time of $45 \mu s$. The properties for the background medium were set to lossless water, while the layer of skull bone was assigned the properties of bone. The skull was defined as a circular disc with an outer radius of 8.75 cm and a thickness of 6.5 mm. The source was defined as a 30 mm line source with a 30 mm focal length (defined using electronic delays). The source signal was a 3 cycle tone burst centred at 0.5 MHz and was injected as a velocity source.



Figure 23. Simulation of the transmission of ultrasound waves generated by a focused transducer through a layer of skull bone. The upper three panels show snapshots of the normal stress. The position of the skull layer is denoted using the dashed lines. The lower two panels illustrate the temporal maximum value of the particle velocity magnitude recorded at each grid point over the duration of the simulation both with, and without absorption.

Three snapshots of the evolution of the wavefield are shown in Figure 23 (parts a - c), with the position of the skull layer outlined with the dashed lines. The temporal maximum of the particle velocity magnitude recorded at each grid point during the simulation is shown in part d. For comparison, the equivalent result calculated using a lossless elastic wave model is shown in part e. When absorption is included, the magnitude of the particle velocity in the focus (shown with the black crosses) is reduced by 30%. This is particularly significant for therapeutic applications of ultrasound in the brain, such as transcranial neurostimulation, and MR-guided focused ultrasound surgery. Studying the magnitude and distribution of ultrasound within the skull under different sonication conditions is one potential future application of the model.

3.4.5 Heat generation in bone

To calculate the heating inside bone, the elastic wave models must be coupled with a thermal model. The purpose of this work was to develop new thermal models that can be easily coupled to the elastic wave models in a computationally efficient way. A pseudospectral solution to the heat diffusion equation (in the form of Pennes' bioheat equation) was implemented within the framework of the k-Wave toolbox. This allows the diffusion and perfusion of heat in heterogeneous tissue to be calculated. The model is exact in the case of homogeneous media, and gives high accuracy for low computational cost in the case of heterogeneous coefficients. This allows the heating of bone tissue under different sonication conditions to be studied. The code was validated against the Green's function solution to Pennes' bioheat equation in 1D, 2D, and 3D. For



heterogeneous media, the code was validated by using piecewise heterogeneous media and comparing the solutions in each region with the corresponding Green's function solution.

The developed elastic and heat diffusion models were then coupled together and used to investigate the effect of different heating mechanisms when ultrasound is incident on bone. For reference, the simulations were also performed using the fluid model in k-Wave (kspaceFirstOrder2D) to examine the heating when shear waves are ignored. The final temperatures for a sonication angle of 45° for two transducer configurations are shown (see Figure 24).

At normal incidence, the final temperature was almost identical for both the fluid and the elastic models. At this angle of incidence, there was very little mode conversion from compressional to shear waves, thus neglecting the contribution of shear wave absorption had a negligible effect on the temperature estimation. As the incidence angle was increased to 45°, the generation and absorption of shear waves became the dominant contribution to the volume rate of heat deposition. Consequently, there was a significant difference in the temperature maps when shear waves were included or neglected (see Figure 24 below). For the material properties used, the critical angle for the compressional wave assuming plane wave incidence is ~31°. Thus, beyond this angle, the fluid model incorrectly predicts that a large component of the acoustic energy is reflected from the bone surface, resulting in almost no temperature change inside the bone layer.





3.4.6 Conclusion

The activities in this objective led to collaboration between NMIs and academia, therefore disseminating ideas and techniques, which laboratories had built-up over many years and enabling new capacities for NMIs. The emphasis on the importance of computational modelling of acoustic, thermal and dose fields will accelerate the development of treatment planning software, leading to greater clinical uptake of a new technology. It is envisaged a number of projects will follow up on the code developed within this project.

Linear acoustic holography has been established as the preferred method of providing acoustic input data for field and exposure modelling. This was developed by MSU and further tested by NPL and PTB. An agreement between calculated and measured fields within approximately 2% for pressure magnitude was achieved.

To provide enhanced field and exposure modelling, a high performance workstation (24 cores, 256GB memory) has been installed at NPL and a 3D Westervelt model (Wave3D) has been implemented to run on



this: it takes acoustic hologram data as the field input and used an operator-splitting approach to calculate the nonlinear field with an arbitrary number of harmonics. The model also includes shock-wave heating and is linked to a thermal solver which can also model heat losses due to bloodflow.

Bone is becoming an increasingly important consideration for optimized treatment planning as the range of conditions amenable to treatment with ultrasound increases. The Kelvin-Voigt visco-elastic models developed by UCL are an important advance in providing calculation tools for users. The heating results demonstrate the importance of shear waves in the calculation of ultrasound heating in bone for non-normal incidence, as well as the utility of the developed elastic wave and thermal models. In the future, these coupled models could be used to study clinically relevant bone anatomies and treatment protocols to give insight into therapeutic ultrasound therapies involving bone.

3.5 Development of methods to improve the accuracy of the individual treatment including use of anatomical data.

3.5.1 Introduction

For individual treatment to be successful, it is important to understand the factors which distinguish the treatment of an individual patient from some idealized and simplified model. Work carried out under this objective has examined some of these factors. The work has addressed interaction between the body and physiotherapy sources (3.5.2), the use of anatomical data within propagation models to improve treatment planning between ribs (3.5.3), a system for delivering controlled and accurately measured thermal doses to cells (3.5.4) and the biological relevance of thermal dose on cell behaviour and survival (3.5.5 and 3.5.6). Eight related papers have been published.

3.5.2 Changes in the field distribution for physiotherapy transducers when in contact with skin mimics compared to the free-field distribution

It is well known that physiotherapy systems typically have resonant transducers which can be sensitive to the acoustic load presented by the medium into which they radiate and that the power output can change when coupled to a membrane. Therefore it is interesting to investigate if the presence of these membranes, also affects the radiation pattern of the physiotherapy transducers.

To carry out the evaluation, CSIC has done measurements using a hydrophone scanning tank on several systems, composed of a calibrated transducer connected to a signal generator and a power amplifier (Figure 25). Measurements in terms of acoustic pressures have been made at 1 MHz and 3 MHz; silicone rubber of different thickness provided by NPL have been used as the skin mimicking layers. Besides direct contact situations, the membranes have been placed at a range of distances from the transducer radiating surface. For all the membrane positions, and



Figure 25. Partial view of the measurement set-up at CSIC showing the transducer (top), circular membrane, and needle hydrophone (bottom).

for each combination of physiotherapy transducer and membrane, the different beam acoustic axes have been localized and the corresponding axial beam pressure distribution have been determined, following the procedures given in the IEC 61689, the relevant standard for the characterization of physiotherapy systems. From this, perpendicular lateral beam profiles at different relevant points on the acoustic axes, identified from the beam axial pressure distributions, have been carried out.

Careful analysis of all these profiles, obtained from three different physiotherapy transducers operating at two frequencies, in combination with three different membranes of different thickness, 0,5 mm, 1 mm, and 1,5 mm and over a range of distances. There has not been found evidence of relevant changes in the field distribution



of any of the physiotherapy transducers tested when in contact with skin mimics in comparison with the freefield distribution. In most cases, only minor amplitude changes, compatible with absorption in the membranes, have been detected.

3.5.3 **Treating between ribs**

The liver is a common site of occurrence for both primary and secondary tumours and hepatocellular carcinoma, the most common form of liver cancer, which is the third most common cause of cancer related death worldwide. One of the difficulties which currently hinders the more widespread clinical application of HIFU in the context of trans-costal treatment is the transmission of sufficient energy through the ribcage to induce tissue necrosis at the required location whilst minimising the formation of side lobes. This is also for renal and pancreatic tumours. Furthermore, rib bones both absorb and reflect ultrasound strongly and a common side effect of focusing ultrasound in regions located behind the ribcage is the overheating of bone and surrounding tissue, which can lead to skin burns. The successful treatment of intra-abdominal cancers requires a thorough understanding of the way in which the ultrasonic pressure field from a HIFU array is scattered by the ribcage.



z plane (right, rib cross-sections shown in grey) resulting from field of 1 MHz multi-element array focused using a constrained optimization algorithm.

In 2011, NPL published a boundary element method (BEM) approach to modelling the scattering by human ribs of the field of a HIFU array, where the advantages of BEM compared to other numerical schemes were highlighted. Subsequently, as part of the this project, this forward model was reformulated as an inverse problem, whereby the HIFU array element surface normal velocities were optimized so that the acoustic pressure magnitudes on the surface of the ribs remained below a specified threshold (Figure 26). The work was further developed to include a surface impedance boundary condition on the ribs, thus overcoming limitations of the earlier model. An approach based on a Generalized Minimal Residual Method (GMRES) implementation of the Helmholtz integral equation BEM formulation was developed and validated. This was used to model the scattering of the field of a multi-element HIFU transducer by locally reacting 3D objects of an arbitrary geometry under continuous wave excitation. This has been specifically applied to both human and idealized ribs.



Using BEM as the forward model, focusing through the ribs was investigated on six array-rib configurations employing a range of focusing methods (Table 3). These included spherical focusing, binarized apodization based on geometric ray tracing, phase conjugation, DORT (short for Decomposition de l'Operateur de Retournement Temporel, also called

Table 3.	Peak focal	pressure	the for	six array-	rib configui	ations and for all
methods	of focusing.					

Array-rib configuration	Spherical focusing	Binarized apodization	Phase conjugation	DORT	Constrained optimization
1	3.2 MPa	3.0 MPa	2.7 MPa	2.1 MPa	3.1 MPa
2	3.4 MPa	3.2 MPa	2.8 MPa	2.0 MPa	3.4 MPa
3	1.7 MPa	1.3 MPa	1.2 MPa	0.97 MPa	1.7 MPa
4	3.0 MPa	2.7 MPa	2.1 MPa	1.6 MPa	3.0 MPa
5	2.3 MPa	1.8 MPa	1.9 MPa	1.2 MPa	2.3 MPa
6	2.0 MPa	0.70 MPa	1.2 MPa	0.68 MPa	1.8 MPa

time-reversal), and constrained optimization. The rib topology was obtained from an adult male human cadaver. The increase in specific absorption rate (SAR) as one criterion used to evaluate the efficacy of the focusing methods. Another criterion was the focal acoustic pressure relative to the upper limit of the array's dynamic range. Whilst the phase conjugation approach maximised the SAR gain on the configurations investigated, it consistently resulted in focal pressures lower than those produced by the constrained optimization method. This may be an issue if the phased-array does not have a wide enough dynamic range that the source velocities may be increased sufficiently to produce the focal pressure magnitudes required for tissue ablation. From a treatment planning point of view, the constrained optimization is likely to provide greater flexibility than phase conjugation, particularly if patient-specific acoustic dose rates are established for safe and efficient treatments, along with damage thresholds.

3.5.4 Cell heating system

Thermal therapies such as radiofrequency, microwave ablation and HIFU involve heating biological tissues to temperatures in excess of 60 °C for short times of the order of a few seconds in order to destroy the cells in a given target region. For thermally mediated effects, it is important to establish the optimal thermal dose and the temperature at which it should be delivered, where the desired biological effect is achieved. Knowledge of the response of cells to heating as a function of temperature and time is also needed to establish more rigorous planning of thermal treatments.

A novel system (shown schematically in Figure 27) has been developed at NPL for delivering controlled and accurately measured thermal doses (with an uncertainty of 20% in thermal dose) to cells in culture



Figure 27. Experimental set up of cell heating chamber under confocal microscope.

under real time light microscopy, which enables monitoring of morphological changes in cells as an indicator of thermal damage. The basis of the system was a coverslip (No. 1.5, 170 µm D 263 M Schott glass; Ibidi GmbH, Germany) with a 30 Ohms/sq coating of Indium Tin Oxide (ITO) (coating by Diamond Coatings Ltd., Halesowen, UK) forming a transparent electrode to allow delivery of heating during optical microscopy. Screen printed silver electrodes were applied to the ends of the slide (also by Diamond Coatings Ltd., as above) to provide contact connections for the delivery of electrical current. Spatial uniformity of the temperature across the slide surface was evaluated using infrared imaging. The base of a coverslip with well chambers assembled on top was coated with black paint to reduce reflections, then imaged from below using an infrared camera (Optris PI200 Thermal Imager, Optris GmbH, Berlin, Germany) as the slide was heated.

To avoid condensation on the lid of the well chamber during heating, which would affect image quality, a heated lid was used. A 3D printed stage insert for the microscope was designed to accommodate two slides with cell culture wells, one of which was heated, the other served as a control to enable simultaneous tracking of both populations: the stage insert also carried the electrical connections and was covered by a CO₂ flow enclosure.





Figure 28. DIC images of adherent HeLa cells in culture, cells exposed to 46.5 °C for 20 minutes resulting in a thermal dose of 240 cumulative equivalent minutes. (a) Cells before heating; (d) Same region 18 hours after heating. Change in fractional image area covered by cells in the image for heated and control cells.

Cells were imaged on an inverted confocal laser scanning microscope (FV1000, Olympus, Southend-on-Sea, UK). Time lapse images of live cells in the heated and control slides were acquired using differential interference contrast with a 10x / 0.4 objective lens (UPLSAPO, Olympus, as above). One area on each of the heated and control slides was imaged during each experiment. In order to accommodate thermal drifts due to heating of the chamber, a Z stack of images was acquired at each time point for the heated slide and the image with the greatest normalised variance in pixel values was selected as the in focus slice. Once the in focus slice had been selected from the Z stack at each time point, texture analysis was performed using a standard deviation filter to identify the cells in the images. The fraction of the image area covered by cells was calculated from ratio of the sum of this threshold mask to the total number of pixels in the image. Preliminary results showed morphological changes in HeLa cells exposed to thermal doses of between 60 and 230 equivalent minutes at 43°C at temperatures of between 44.5 C and 52.5 C. Cells shrank in area and became more rounded in shape and cytoskeletal actin filaments were disassembled (see Figure 28 above).

In this work, efforts were made to understand the temperature distribution that cells were exposed to and to minimise the uncertainties in thermal dose. Measurement of the temperature of small volumes of material in which the temperature is changing rapidly is extremely challenging. For these type of measurements the cell monolayer will be significantly thinner than most sensors although the area covered may be much larger. This will create errors in the measured temperature while there are rapid changes in temperature during heating and cooling. Fine wire thermocouple temperature measurements were validated against reference sensor measurements. Temperature was measured with the accuracy required for calculating thermal dose with an uncertainty less than 20%.



3.5.5 Methodology for cell monolayer models suitable for thermal and ultrasound exposures, with appropriate biological assays

The thermal dose, EM₄₃, (in units referred to as equivalent minutes at 43 °C), was introduced to relate the exposure of tissues to increased temperatures, held for different lengths of time, to a given biological endpoint. The widely accepted EM₄₃ formulation suggests that, for each °C increase in temperature above 43°C, the treatment time should be halved to achieve the same cytotoxic effect. The accumulated thermal dose is given by:

$$EM_{43} = \sum_{t=0}^{t=final} R^{(43-\bar{T})} \Delta t$$

where \overline{T} is the average temperature during time Δt , R=0 for temperatures < 39°C, 0.25 for temperatures between 39°C and 43°C, 0.5 for temperatures > 43°C. In practice, three phases can be seen in a typical temperature profile: an initial heating period, a period of approximately constant temperature, and a cooling period.

To study the range of applicability of this relationship, a novel heating bath method which allows temperature determination in real time, and thus permits determination of variations in thermal dose delivery for short (< 5 second) exposures at higher temperatures was developed. In addition, a high precision device for cell thermal cycling, which allowed high precision thermal dose estimation for longer (> 32 seconds)



exposures at lower temperatures, was used. The effects of thermal exposures in models of colon adenocarcinoma in-vitro at times up to 14 days after the thermal insult were investigated. The cytotoxic effects of "rapid" thermal exposures at temperatures above 55°C were compared with the effects seen when the same thermal dose was delivered over a longer period of time at temperatures in the range 46-54°C. Using this technique, it was observed that:

- Cells can withstand an EM₄₃ of 240 minutes by remaining in a non-adherent "dormant" state for several days, while retaining their proliferative potential.
- The EM₄₃ is a reasonable predictor of cell viability for long duration thermal exposures (\geq 32 seconds).
- A novel technique for rapid heating of cells has been demonstrated in practice.
- Cells subjected to short, high temperature exposures exhibited greater resistance to the heat treatment than those exposed to a longer, lower temperature regime for the same EM₄₃ (see Figure 29 above).

Overall, the relationship has been tested and found to provide a reasonable prediction of thermal damage for temperatures up to 47° C, the range for which it was originally formulated. However, there is evidence from these studies that short exposures are less toxic than expected according to the relationship commonly used and that the thermal dose threshold used in the clinic needs to be adjusted to 500 minutes EM₄₃ to achieve sustainable cell death over a long time period.



3.5.6 Survival curves and histological results

3.5.6.1 For cells heated using electrical current

Heat induces pleiotropic biological effects. The cytotoxic effects of hyperthermia have been associated with i) necrotic cell death, ii) induction of apoptosis, and iii) cell cycle arrest. The earlier findings that the measured cytotoxic effect of heat on cancer cells depends on time elapsed after treatment is suggestive of the activation of programmed cell death pathways. It was therefore of interest to investigate the programmed cell death processes induced in colon cancer cells in response to a range of EM₄₃ (0 to 240 EM₄₃) in order to understand how the fate of heated cells was divided between these possible paths.

Increases in EM₄₃ achieved using temperatures in the range $45 - 47^{\circ}$ C, were observed to result in: a) induction of apoptosis; b) induction of autophagy that correlated with the response of live cells to treatment; c) an increase in RIPK3 protein levels, suggesting that necroptosis may be associated with the EM43-induced cellular response; d) transient cell cycle arrest. Based on these findings, a map was created showing the percentage of cells undergoing the different distinct programmed cell death processes in the same cell population as



shown below (TD = EM_{43}). The percentage of cells that appeared to be normal on the previous day, undergoing different cell death processes is shown graphically in Figure 30.

3.5.6.2 For cells heated using a water bath while exposed to ultrasound

To investigate whether cells respond differently to heating caused by ultrasound compared to heating in the absence of ultrasound, an ultrasound exposure chamber was developed (see Figure 31). Using this chamber, cells cultured either as a monolayer or in 3D gel matrices can be exposed to ultrasound at variable intensities. The apparatus consists of an automated gantry on which is mounted a 1.66 MHz transducer, and a water tank holding in place an acoustic 15-well plate consisting of 3x5 wells. An acoustic interface is provided by sealing the acoustic plate with Melinex film. The automated gantry is connected to a HIFU signal generator and a motion controller. The apparatus is controlled from a laptop and can record cavitation events.

Using this set-up, control and pre-heated cells were treated with 1.66 MHz HIFU beams of different intensities for 5 seconds. Cytotoxicity was then determined. Preliminary data indicates that the major cytotoxic effect is due to the thermal exposures of cells and not due to the non-thermal ultrasound effects.





3.5.7 Conclusion

Looking for changes in the field distribution of physiotherapy transducer tested when in contact with, or close to, skin mimics, evidence of significant changes from the free-field distribution has not been found. In most cases, only minor amplitude changes, compatible with absorption in the membranes, have been detected. This gives confidence that the distribution of the acoustic field measured in water can be used as the basis for determining the field inside the body (and hence for planning treatments), even for resonant physiotherapy transducers.

Many intra-abdominal cancers lie inside or close to the ribcage or spine. Treating these optimally requires a thorough understanding of the way in which the ultrasonic pressure field from a HIFU array is scattered and absorbed by bone. The Boundary Element method using a GMRES implementation of the Helmholtz integral has shown that modelling the scattered field of a multi-element transducer is feasible and has demonstrated a method by which the treatment field can be tuned to match the individual patient. Of course, much work is still required to be able to do this in a timeframe which is more useful clinically.

Looking at monitoring the effect of heat on cells, NPL developed a system for delivering accurately quantified thermal doses to cells in culture while monitoring changes in realtime using DIC microscopy during heating and for up to 24 hrs afterwards. The system can be used to quickly compare the responses of different cell lines to locate damage thresholds and determine temperature time combinations for further investigation using immunohistochemical assays. Further data is required to evaluate the dose response for different cells but this data can ultimately be used to inform planning or thermal therapies with more accurate dose response data.

Overall the work by ICR has tested the widely used thermal dose relationship and found it to provide a reasonable prediction of thermal damage for temperatures up to 47°C, the range for which it was originally formulated. However, cells treated with "rapid" thermal exposures exhibited greater resistance to the heat treatment than cells subjected with "slow" thermal exposures for the same EM₄₃. These results may have a significant impact on HIFU applications in the clinic. The data suggest that the thermal dose threshold used in the clinic needs to be adjusted to 500 minutes EM₄₃ to achieve sustainable cell death over a long time period.

Other results suggest that therapies targeted on intracellular molecules may enhance the cytotoxic effect of HIFU. For example data demonstrated synergistic cytotoxic effects of HIFU with targeted inhibitors of the Hsp90 molecular chaperone. In addition, the ultrasound exposure chamber provides a biologically and acoustically compatible system in which 2D and 3D cell cultures can be exposed to HIFU. The chamber can be developed further to allow recording of temperature history and thermal dose calculation.



Actual and potential impact

3.6 Overview

Beneficiaries

The long term aim of this project is to benefit i) patients by providing more effective therapy based on personalised treatment planning; ii) doctors, medical staff and healthcare providers by reducing the cost and improving efficiency of treatment delivery and; iii) medical equipment manufacturers and suppliers by easing the acceptance of novel therapies into the market.

Dissemination

Overall 49 scientific papers have been published or accepted for publication and with 69 conference presentations. A special session on 'Field Characterization and Dosimetry for Therapeutic Ultrasound Applications' was held at the Acoustical Society of America conference, a key international conference for ultrasound physicists. Workshops and symposia were also held with project partners presenting to 30 participants from the metrology, standards and regulatory communities. Two special issues of the International Journal of Hyperthermia were published which included 8 papers authored by DUTy partners. Two books based on this work have been commissioned and will include chapters or be edited by project participants.

Impact on standardisation

The outputs from this project contributed to the development of a common language and a metrological infrastructure (basic definitions, validated measurement methods and validated modelling methods) for ultrasound dosimetry. These new capabilities have been disseminated widely to the instrumentation, clinical, standards and research communities, and are starting to be used to support the development and validation of ultrasound instrumentation and appropriate standardisation. During the lifetime of this project, there have been inputs to draft documentary standards IEC62556 & IEC62555 and published regulation IEC60601-2-37. There has been substantial impact on standardisation in IEC TC87 (Ultrasonics) and IEC SC62D (Electromedical therapeutic equipment). The UK and USA national committees have submitted two proposals related to therapeutic ultrasound to IEC TC87 (one on acoustic holography and field modelling; the other on high pressure field measurement). Another proposal on calibration of HITU hydrophones is currently under consideration.

Early impact

This project has enhanced the European measurement infrastructure for therapeutic ultrasound. The capabilities developed have been disseminated to the instrumentation, clinical, standards and research communities and are already starting to be used by the project participants and stakeholders to support the development and validation of ultrasound instrumentation and appropriate standardisation.

- NPL has established a measurement consultancy service for HIFU equipment which includes measurement of acoustic and electrical power, acoustic holography measurements to IEC62556, and modelling to support compliance with IEC60601-2-62. Measurements have been made for four European and international ultrasound equipment companies.
- PTB has developed a scheme to provide traceability to the German Primary Standard for hydrophones intended to be used for the measurement of very high intensity fields, typical of HIFU therapy systems;
- PTB is exploring the possibility of a collaboration on sensors for medical ultrasound with a manufacturer of cavitation sensors, and has had several requests from customers (mainly manufacturers of HIFU devices) concerning HIFU power measurements according to new IEC62555 Standard.
- HoMe has established a collaboration with an institute in Berlin to calibrate the output intensity of their new custom-designed system which uses ultrasound to stimulate nerve cells. These new capabilities will support the development of HIFU clinical applications and in particular provide confidence in applying defined and well-controlled acoustic exposures for treating a range of the clinical conditions, to the benefit of patients, clinicians and equipment manufacturers.



Long term impact

Manufacturers and regulators need measurement standards to allow them to bring new equipment to market and help to establish a more homogenous global regulatory and purchasing environment. This will give healthcare providers a greater range of reliable therapies available and allow more comparison of data and tailored treatment plans. It is anticipated that the measurement standards and methods developed will provide the basis for rigorous treatment planning of the emerging therapies, which in turn will lead to better, potentially cheaper, disease management, including less invasive treatments with fewer side-effects and shorter recovery times.

4 Website address and contact details

PTB built up a TYPO3-based website and uploaded it to the URL <u>http://www.duty-project.eu</u>. The website contains information about the project and the consortium, public documents, a regularly updated news section and a restricted part for the consortium members.

5 List of publications

5.1 Published

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