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Direct thermal dose control of constrained focused ultrasound treatments: phantom and *in vivo* evaluation

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Abstract

The first treatment control system that explicitly and automatically balances the efficacy and safety goals of noninvasive thermal therapies is described, and its performance is evaluated in phantoms and *in vivo* using ultrasound heating with a fixed, focused transducer. The treatment efficacy is quantified in terms of thermal dose delivered to the target. The developed feedback thermal dose controller has a cascade structure with the main nonlinear dose controller continuously generating the reference temperature trajectory for the secondary, constrained, model predictive temperature controller. The control system ensures thermal safety of the normal tissue by automatically complying with user-specified constraints on the maximum allowable normal tissue temperatures. To reflect hardware limitations and to prevent cavitation, constraints on the maximum transducer power can also be imposed. It is shown that the developed controller can be used to achieve the minimum-time delivery of the desired thermal dose to the target without violating safety constraints, which is a novel and clinically desirable feature. The developed controller is model based, and requires patient- and site-specific models for its operation. These models were obtained during pre-treatment identification experiments. In our implementation, predictive models, internally used by the automatic treatment controller, are dynamically updated each time new temperature measurements become available. The adaptability of internal models safeguards against adverse effects of modelling errors, and ensures robust performance of the control system in the presence of *a priori* unknown treatment disturbances. The successful validation with two experimental models of considerably different thermal and ultrasound properties suggests the applicability of the developed treatment control system to different anatomical sites.

1. Introduction

Focused ultrasound thermal therapies are a promising noninvasive treatment modality for tissue ablation and hyperthermia used in conjunction with radiation and chemotherapies. The feasibility of high-intensity focused ultrasound (HIFU) therapies to noninvasively ablate spatially distributed targets inside the patient has been demonstrated in several studies (Poissonnier *et al* 2003, Uchida *et al* 2002, Hynynen *et al* 2001, Wu *et al* 2001.). For instance, Hynynen *et al* (2001) used high temperature (up to 90 °C) MR-guided ultrasound surgery to noninvasively coagulate benign breast fibroadenomas. The benefits of low temperature (in the range of 41–42 °C) therapies in combination with radiation (Guthkelch *et al* 1991) and chemotherapy (Bornstein *et al* 1993) have also been reported in various clinical trials. For a comprehensive review on ultrasound thermal therapies, see Diederich and Hynynen (1993).

The lack of adequate control of noninvasive delivery of heat has been identified as an obstacle to widespread use of thermal therapies (Bouchard and Bronskill 2000, Salomir *et al* 2000). Thus, the development of an advanced automatic feedback treatment control system is a significant challenge and opportunity, complementary to the development of improved treatment hardware and planning. In a conventional clinical setting, the thermal treatments rely to a large extent on past experience, results of computer simulations, animal experiments and intra-treatment manual control based on temperature feedback. Compared to the traditional approach, online automatic feedback control of thermal treatments potentially offers a number of advantages including:

- i. robustness with respect to patient-to-patient variability and various treatment disturbances, such as changes in temperature-dependent ultrasound absorption (Worthington and Sherar 2001, Worthington *et al* 2002) and tissue perfusion (Akyurekli *et al* 1997);
- ii. normal tissue safety;
- iii. reduced treatment time.

However, a treatment control system, which would allow a physician to concentrate on clinically relevant objectives, while automatically performing low-level tasks of interpreting measurements and selecting appropriate ultrasound excitation, is yet to be developed. Our progress towards such a system is the focus of this paper.

The automatic control requires the translation of clinically relevant treatment *efficacy* and *safety* objectives into well-defined and achievable control objectives. The efficacy objectives can be formulated as either temperature control, or the direct thermal dose (TD) control problem. Previously, Salomir *et al* (2000) attempted to control temperature based on MR thermometry and spiral path scanning of an ultrasound focal zone. In a simulation study, Vanne and Hynynen (2003) showed the feasibility of a MR thermometry based LQR controller to achieve a desired temperature–time profile in a single point of interest. The pointwise control of temperature distribution is generally impossible with the currently available noninvasive heating modalities, though hardware improvements can provide additional degrees of freedom in manipulating specific absorption rates (SAR), which would improve control of temperature distribution in the spatially distributed target. On the other hand, control of thermal dose is possible, and it is achievable with a broad range of transducers, including phased arrays and focused ultrasound transducers.

The treatment controllers, which explicitly satisfy the imposed normal tissue safety constraints while achieving treatment efficacy, have received recent attention. In our approach, a controller is designed to achieve treatment efficacy, expressed as the desired thermal dose delivered to the tumour, without violating safety constraints, formulated as the peak allowable temperatures in selected normal tissue locations. The safety constraints are imposed to minimize patient pain, discomfort and damage to the healthy tissue.

In an initial attempt to develop such a controller, Arora *et al* 2002 demonstrated the first ever direct feedback control of thermal dose. The developed controller was based on continuous linearization of thermal dose relationship, and used a linear model predictive controller to deliver a desired dose to the tumour, subject to temperature constraints in the surrounding normal tissue. The linearized TD relationship limited the applicability of the first generation thermal dose controller to relatively low (8–10 °C) temperature elevations. In the subsequent works (Arora *et al* 2005a, Arora *et al* 2004), a novel direct thermal dose controller was developed that is equally applicable to low and high temperature therapies. This improved thermal dose controller has a cascade structure with a main nonlinear thermal dose controller

that dynamically generates reference temperature trajectories for a secondary, constrained model predictive temperature controller.

In this paper, the approach of achieving treatment efficacy and safety by directly controlling the desired thermal dose without violating peak normal tissue temperature is experimentally demonstrated for the case of a stationary, focused ultrasound transducer used to sonicate agar phantom and *in vivo* canine subject. The experimental results demonstrate that direct control of thermal dose without violating safety constraints is possible and practical.

2. Methods

A brief description of the thermal and ultrasound modelling procedure and the developed nonlinear thermal dose controller is presented in this section. The detailed controller description can be found in Arora *et al* (2005a), which also describes its evaluation using computer simulations.

2.1. Thermal dose

The concept of the thermal dose has been proposed to quantify the relationship between treatment efficacy and the target temperature as a function of time. Sapareto and Dewey (1984), based on extensive experimental results with cell cultures, proposed the following relationship between the tissue thermal dose $D(t)$ (also known as cumulative equivalent minutes, CEM, at 43 °C) as a function of treatment temperatures, $T(t)$, and time t :

$$D(x, y, z; t) = \text{CEM at } 43^\circ\text{C} = \int_0^t R^{[43 - T(x, y, z, \tau)]} d\tau \quad (1)$$

where the empirical constant R is given by

$$R = \begin{cases} 0 & \text{for } T < 39^\circ\text{C} \\ 0.25 & \text{for } 39 < T < 43^\circ\text{C} \\ 0.5 & \text{for } T > 43^\circ\text{C} \end{cases} \quad (2)$$

Because a limited number of measurements have been available clinically, investigators in the past used a single thermal dose for the entire target, rather than using a pointwise thermal dose definition given by equation (1). Dewhirst and Sneed (2003) summarize the various measures of thermal dose that have been used to characterize the treatment outcome. For example, measures such as percentile value(s) or moment(s) of the temperature distribution, $T(x, y, z; t)$, have been correlated to the outcome of the thermal treatments. In this paper, a widely accepted thermal dose definition, based on 10th percentile (Leopold *et al* 1993) cumulative equivalent minutes $\text{CEM}_{43^\circ\text{C } T_{90}}$, is used to characterize treatment efficacy:

$$D(t) = \text{CEM at } 43^\circ\text{C } T_{90} = \int_0^t R^{[43 - T_{90}(\tau)]} d\tau \quad (3)$$

where T_{90} is the 10th percentile temperature of the target.

2.2. Thermal model of phantom and canine thigh

The thermal transport processes in the phantom and *in vivo* canines along the length of the thermocouple probe array are modelled using the one-dimensional Pennes' bioheat transfer equation (Pennes 1948):

$$\rho C \frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2} - W_e C_b (T - T_a) + Q, \quad (4)$$

where C and C_b are specific heat of tissue and blood ($\text{J kg}^{-1} \text{ } ^\circ\text{C}^{-1}$) and W_e ($\text{kg m}^{-3} \text{ s}^{-1}$) is the effective blood perfusion parameter. When a one-dimensional model is used to describe an essentially three-dimensional target, the identified W_e also includes the contribution of the heat conduction in two neglected directions. Consequently, W_e is non-zero for unperfused phantom. T_a is the baseline (equilibrium) temperature, which, in this study, is equal to the steady state temperature of the phantom before the ultrasound energy is applied, or the arterial temperature in the *in vivo* experiments. Q [W m^{-3}] is the power deposited in the tissue using ultrasound sonication. Handbook values (Chato and Lee 1998) for conductivity $k = 0.7 \text{ W m}^{-1} \text{ } ^\circ\text{C}^{-1}$, density $\rho = 1000 \text{ kg m}^{-3}$ and specific heat $C = C_b = 4186 \text{ J kg}^{-1} \text{ } ^\circ\text{C}^{-1}$ are assumed. The values of the perfusion parameter, W_e , and the power deposition, Q , are identified experimentally as described in section 2.5. It is further assumed that $T = T_a$ at the boundaries of the considered treatment domain. In both phantom and canine experiments, the length of the domain is selected to be 7 cm, which is large enough to ensure near-constant boundary temperatures during the heating with the focused transducer.

Using a finite difference approximation of the spatially distributed model (4), the predictive model of the target's thermal response to the ultrasound heating is expressed in the standard state-space form

$$\dot{T} = AT + Bu \quad (5)$$

$$T_{\text{mea}} = CT, \quad (6)$$

where A is the system matrix, which depends on both conduction and perfusion. The state T in equations (5)–(6) is a vector of deviation temperatures above T_a in 71 mesh nodes of the model. The term Bu approximates the power deposition term, where u is the applied ultrasound power in watts. The position of the ultrasound transducer is fixed for each experiment and the applied ultrasound power u is the only manipulated variable. The temperatures in the phantom and canine are measured in seven spatial locations, described by the output matrix C .

2.3. Thermal dose controller

The structure of the developed thermal dose controller is depicted in figure 1. At time t_k , the temperatures $T_{\text{mea}}(k)$, measured in seven spatial locations inside the phantom or canine patient, P , are used in a cubic spline filter, E , to estimate the temperature distribution for the entire spatial area of interest. The estimated temperature distribution, $T_f(k)$, is an input to the block S , which selects the T_{90} temperature of the target. T_{90} is then fed back to the secondary (inner) temperature controller, K_T . Block H is used to estimate, according to equation (3), the thermal dose, D , delivered to the patient up to the current time t_k . D is used as the feedback signal of the main (outer) thermal dose control loop. The difference between D and the desired final dose D_f is used in the nonlinear controller K_D , to compute the reference trajectory $T_{90,\text{ref}}(t)$, $t \in [t_k, t_f]$, as described below (equation (11)).

The outer loop thermal dose controller, K_D , is designed to map the difference between the desired final dose, D_f and the current delivered thermal dose, $D(t_k)$, into the reference 10th percentile temperature trajectory, $T_{90,\text{ref}}$:

$$K_D: [D_f - D(t_k)] \rightarrow T_{90,\text{ref}}(t), t \in [t_k, t_f]. \quad (7)$$

The reference trajectory is such that $D[T_{90,\text{ref}}(t)] \rightarrow D_f$ as $t \rightarrow t_f$ provided that $T_{90,\text{ref}}(t)$ is precisely tracked by the temperature controller, K_T . The map (7) is implemented using two inverse operators $\mathcal{M}_1$ and $\mathcal{M}_2$:

$$K_D[D_f - D(t_k)] = \mathcal{M}_2[\mathcal{M}_1(D_f - D(t_k))] = T_{90,\text{ref}}(t), \quad (8)$$

where $\mathcal{M}_1$ maps the remaining dose deficit, $D_f - D(t_k)$, at each sampling instant onto a reference dose trajectory $D_{\text{ref}}(t)$; $\mathcal{M}_2$ maps $D_{\text{ref}}(t)$ onto the reference $T_{90,\text{ref}}(t)$. Since there are infinitely many reference dose (and temperature) trajectories that will result in the same final desired dose, D_f , the uniqueness of the map $\mathcal{M}_1$ is ensured by using the following linear parametrization of the $D_{\text{ref}}(t)$:

$$D_{\text{ref}}(t) = D(t_k) + \alpha(t_k)[t - t_k]. \quad (9)$$

The slope α is calculated based on the difference between the delivered and the desired thermal dose, and the selected final treatment time:

$$\alpha(t_k) = \frac{(D_f - D(t_k))}{(t_f - t_k)}, \quad (10)$$

where $t_f = t_k + \Delta t$, and the tuning parameter Δt is the *moving treatment horizon*.

With the obtained D_{ref} , $\mathcal{M}_2$ is simply the inverse of the integral equation (3), resulting in the following reference temperature trajectory:

$$T_{90,\text{ref}}(t) = \frac{1}{\ln(1/R)} \ln \frac{\alpha(t_k)}{R^{43}}, \quad t \in [t_k, t_k + \Delta t], \quad (11)$$

which is updated each time a new thermal dose estimation becomes available.

To minimize the treatment time, the particular form of the thermal dose parametrization is not important as long as the corresponding reference temperature trajectory, $T_{90,\text{ref}}$, generated by the map $\mathcal{M}_2$, is aggressive enough to force the activation of the power or temperature constraints. According to the Pontryagin maximum principle (Lewis and Syrmos 1995), the treatment progression at one of the constraints is the necessary condition for time optimal control. Note, however, that as $D(t_k)$ approaches D_f , $D_{\text{ref}}(t)$ must become less aggressive so that the map $\mathcal{M}_2$ produces an attainable (or nearly attainable) trajectory $T_{90,\text{ref}}(t)$; if this condition is not satisfied, then the overall thermal dose delivered during the treatment will exceed the desired value and result in a longer than optimal treatment time. Our earlier work (Arora *et al* 2005a, 2004) shows that with an appropriate selection of the moving treatment horizon Δt , the parametrization (9) leads to a near time-optimal treatment.

The $T_{90,\text{ref}}(t)$ trajectory, obtained as the output of the thermal dose controller K_D , serves as the reference for the inner temperature controller K_T . To ensure that the maximum allowable temperature in the selected spatial location of the normal tissue is not violated, K_T is implemented as a linear, constrained, model predictive controller. The predictive nature of the temperature controller also allows it to estimate the dose that will be accrued at the end of the treatment after the power is turned off. By taking into account the dose delivered during cooling, which can be substantial during high temperature therapies, target overdosing is avoided and the minimum treatment time becomes possible.

The predictive model used in K_T is given by equations (5) and (6). K_T is the optimizing controller that generates the m future control moves, $\mathbf{u} = [u(k), \dots, u(k+m-1)]$ by solving the following optimization problem:

$$\min_{\mathbf{u}} J(k) \quad (12)$$

subject to the process model (5)–(6), and temperature and actuation constraints:

$$T_n(k+j) \leq T_{n,\max} \quad j \in [1, p] \quad (13)$$

$$0 \leq u(k+j-1) \leq u_{\max} \quad j \in [1, m], \quad (14)$$

where $T_{n,\max}$ is the maximum allowable temperature in the selected location x_n of the normal tissue, and $u_{\max}$ is the transducer saturation limit. The quadratic objective function J is defined as

$$J(k) = \sum_{j=1}^p w_y(j) [T_{90,\text{ref}}(k+j) - T_{90}(k+j)]^2 + \sum_{j=1}^m w_u(j) [u(k+j-1)]^2, \quad (15)$$

where the weight w_y is used to penalize errors between the desired and the estimated T_{90} , and w_u weighs the penalty on the control effort. The tuning parameters p and m are known as prediction and control horizons, respectively. The horizon p determines the time over which the temperature predictions are made. We typically select the prediction horizon to be long enough to estimate the thermal dose accrued during tissue cooling after the power is turned off. The control horizon m determines the number of future control moves that are calculated each time a new measurement becomes available. Only the first move, $u(k)$, is actually applied to the patient, and the procedure is repeated at the next sampling instant. The effect of the tuning parameters on the controller performance is detailed in Arora *et al* (2005a).

2.4. Experimental setup

The phantom experiments were performed on an $11 \times 11 \times 7$ cm agar phantom prepared to mimic ultrasound absorption and thermal properties of human tissue (Madsen *et al* 1998). The *in vivo* experiments were performed on a German Shorthair's thigh muscle. Anaesthesia was induced using 40 mg Kg^{-1} of Ketamine and 7.5 mg Kg^{-1} of Xylazine and maintained with Forane gas. During phantom and animal experiments, the subject was placed on a thin mylar membrane located on the top of an acrylic chamber filled with degassed and deionized water. The water chamber houses the ultrasound transducer and a 45° ultrasound mirror to reflect the focused beam towards the target. The location of the focal zone inside the target can be adjusted at will in three dimensions by changing the position of the focused ultrasound transducer using a position control system. After the initial alignment, the transducer remained fixed during each series of experiments. To improve the ultrasound coupling, the dog's thigh was shaved, treated with hair removal lotion, and ultrasound gel was applied between the tissue and the mylar window. Plastic bags filled with degassed water were placed between the two thighs to minimize the ultrasound reflections at the tissue–air interface. The schematic of the ultrasound, thermometry and control systems is shown in figure 2 for the case of *in vivo* experiments.

The ultrasound field was generated by a single, spherically focused, air backed transducer resonating at 0.5 MHz. The radius of curvature and the diameter of the transducer used were 20 cm and 7 cm respectively. The details of the transducer circuitry and power measurement

are provided in Arora *et al* (2004). The temperatures in the phantom and the canine muscle were monitored using a seven-sensor manganin–constantan linear thermocouple array, built and calibrated in our laboratory. Temperatures were measured every second. The first thermocouple was positioned approximately 0.5 cm into the phantom or dog thigh. The remaining junctions were located 1 cm apart over the length of the domain, (figure 2). During the experiments, the data acquisition system (National Instruments) was used to measure and display real-time temperatures.

The temperature measurements from data acquisition computer were transferred in real time to a dedicated thermal therapy control computer (figure 2). The computed control signal (transducer's power), measured and estimated temperatures, and the delivered thermal dose were monitored and stored for subsequent analysis. The calculated control signal drives the function generator connected using a GPIB interface card (National Instruments) to the thermal therapy controller.

2.5. Model identification

The perfusion related parameter W_e and ultrasound power deposition density Q are needed for the design of the model predictive temperature controller, K_T . These patient-specific parameters were identified based on temperature measurements provided by seven thermocouples in response to a low-intensity ($2\text{W} < u < 3\text{W}$) step increase in ultrasound power, applied during a pre-treatment heating session. Since conduction and convection effects are negligible immediately after the power is initiated (Roemer *et al* 1985), equation (4) simplifies to

$$\rho C \frac{\partial T(x)}{\partial t} = Q(x). \quad (16)$$

Therefore, Q can be estimated at the measurement locations from the initial slope of the recorded temperatures. A spline fit was then used to obtain the power deposition pattern along the entire length of the target region.

The effective perfusion, $W_e(x)$, was obtained from the measurements of the steady state temperatures reached in response to a step change in ultrasound power. At steady state, equation (4) reduces to

$$k \frac{\partial^2 T}{\partial x^2} - W_e(x) C [T - T_a] + Q(x) = 0 \quad (17)$$

from which spatially-dependent W_e was identified by solving the least squares problem of minimizing the difference between experimental and model-predicted steady state temperatures. The iterations of the least squares algorithm were stopped when the improvement between successive steps was less than 0.1%.

The identified $W_e(x)$ and $Q(x)$ for both agar phantom and canine muscle are shown in figure 3. W_e in the one-dimensional model, equation (4), includes the contribution of heat conduction in the two unmodelled directions, and is, therefore, non-zero for un-perfused phantom. The identified W_e for the canine describes the combined effect of blood perfusion and conduction in the two unmodeled spatial directions.

The depicted power deposition density, $Q(x)$, is for a total power of $u = 2.86\text{ W}$ in the phantom and $u = 2.33\text{ W}$ in the dog. The difference in focal depths in the phantom and canine is mostly caused by the difference in the relative target-transducer location in the two

series of experiments. In the phantom, the region between $x = 3.6$ and $x = 6$ cm was selected as the ‘tumour’, and the maximum allowable normal tissue constraint was imposed close to the ‘skin’ ($x = 0.6$ cm). During the *in vivo* experiments, the region between $x = 2$ and $x = 3.2$ cm was assigned as a ‘tumour’, and the normal tissue temperature constraint was imposed at $x = 1.6$ cm.

3. Results

The controller experiments were carried out with the efficacy objective of delivering CEM43° T_{90} to the designated ‘tumour’ while maintaining the normal tissue temperature in the specified location below the maximum allowable value (safety objective). A number of experimental runs were carried out with agar phantom and canine muscle to analyse the effect of tuning parameters on the controller performance. Though only one set of results is presented for each case, it was found that the effect of controller tuning qualitatively agrees with results obtained in simulations (Arora *et al* 2005a).

3.1. Phantom results

Figure 4 shows experimental results obtained during direct control of thermal dose in an agar phantom. The desired CEM 43° T_{90} of the tumour was set to $D_f = 30$ min. A normal tissue constraint $T(x = 0.6 \text{ cm}) - 10^\circ\text{C}$ was imposed. The power saturation limit was set at $u_{\max} = 40$ W to demonstrate the controller’s ability to achieve treatment efficacy with constrained transducer power. Note that power constraints will always be present in clinical applications to reflect hardware limitations, or to avoid cavitation.

Figure 4(b) shows the measured temperatures from the seven thermocouples. Temperature plots are shown as deviations from thermal equilibrium observed before ultrasound heating. Also shown are the tumour T_{90} , the temperature at the constraint location, T_{cons} , and the reference temperature, $T_{90,\text{ref}}$, generated by the primary thermal dose controller. $T_{90,\text{ref}}$, generated according to equation (11), becomes a setpoint for the secondary temperature controller, K_T . The thermal dose controller K_D is purposely tuned to be aggressive by selecting a small value of the moving treatment horizon $\Delta t = 10$. The resulting aggressive reference trajectory $T_{90,\text{ref}}$ at the beginning of the treatment causes the saturation of the ultrasound power. Towards the end of the treatment, as the delivered thermal dose approaches the desired value D_f , the reference $T_{90,\text{ref}}(t)$ drops to zero, the power is switched off, and the residual thermal dose is delivered during tissue cooling.

The results of figure 4 confirm that treatment evolves with either power or normal tissue temperature constraints active, which is theoretically necessary to achieve minimum treatment time. At the beginning, the thermal dose controller forces the activation of the ultrasound power constraint. At $t = 50$ s (figure 4(b)), the temperature constraint becomes active and the feedback temperature controller, K_T , automatically reduces the ultrasound power (figure 4(a)) to prevent the violation of the safety constraint.

Figure 4(c) shows the evolution of the delivered thermal dose. The desired final thermal dose D_f is accurately delivered despite substantial prediction errors introduced by the one-dimensional model used in the temperature controller. A simplified model reduces computational requirements for real-time implementation of the model-based, optimizing temperature controller, K_T . The adequacy of the predictive capabilities are, nevertheless, evident from the controller’s ability to maintain the treatment at the maximum allowable normal tissue temperature, and the fact that the power is switched off at the right moment ($t = 180$ s), allowing for the residual thermal dose to accrue during tissue cooling.

The thermal dose evolution at seven locations where the temperatures were directly measured is shown in figure 5. A sharp difference in the thermal dose delivered to the tumour and normal tissue is obtained. This result confirms that by explicitly constraining normal tissue temperatures, the dose delivered to the normal tissue can be limited. Therefore, treatment control with automatically constrained normal tissue temperature appears to be a viable approach to ensure safety of thermal therapies. Also note that the pointwise thermal dose (as defined by equation (1)) in some tumour locations is substantially larger than 30 CEM delivered to the target based on T_{90} temperature (equation (3)). A broad range of pointwise doses is the consequence of non-uniform temperature distribution (with the peak temperature inside the tumour reaching $\approx 24^\circ\text{C}$ above the equilibrium, figure 4(b) created by the focused transducer, and a strongly nonlinear temperature–dose relationship.

3.2. In vivo results

In vivo canine experiments were carried out to evaluate the controller performance and robustness in a heterogeneous medium, similar in complexity to clinically relevant cases. The desired thermal dose was set to 20 CEM_{43°} based on T_{90} temperature of the tumour. In the one-dimensional thermal model used in the predictive controller, the spatial domain between $x = 2$ and 3.2 cm was designated as the tumour (figure 3). The maximum allowable temperature elevation of 7°C was imposed at $x = 1.6$ cm. A lower (compared to the phantom case) value of the desired dose and tighter (and clinically more realistic) normal tissue constraint were selected to avoid damage to the muscle. By minimizing tissue damage, we were able to perform multiple tests with the same subject in order to evaluate the effect of various tuning parameters on the controller performance.

Figure 6 depicts the controlled power, all measured temperatures identified by their locations, and the delivered CEM_{43°} T_{90} dose. The controller applies the maximum allowed ultrasound power ($u_{\max} = 15$ W) at the beginning of the treatment when the normal tissue temperature constraint, T_{cons} , is far from being violated. At $t = 48$ s, the temperature constraint is reached, and the controller automatically modulates the power to maintain the constrained temperature close to the maximum allowable value of 7°C .

Compared to the phantom results, the controller in the canine experiments is more active. Rapid changes in the manipulated ultrasound power are the result of larger modelling errors than those present in the phantom case. A similar closed-loop behaviour was observed in simulations (Arora *et al* 2005a) with modelling errors purposefully added to study the performance of the treatment control system. With modelling errors, the controller performs repeated corrections of the applied power to ensure the treatment progression at, or close to, the maximum allowable normal tissue temperature, which is needed to minimize treatment time. The results demonstrate robust performance of the treatment control system, which was able to accurately, and in near optimal time, deliver the specified thermal dose without violating safety constraints.

The results of figure 6 (as well as in the phantom case of figure 4) were obtained with the weight w_p used in the optimization problem (12), set to zero. The use of zero control penalty leads to an active change in the manipulated ultrasound power when measurement noise or time-varying modelling errors are present. Though active control does not present a practical problem in our electronically actuated system, if desired, a smoother power input can be obtained with larger value of w_p . However, a less active control in this case will lead to a longer treatment.

The measured temperature deviations at the seven thermocouple locations are depicted in figure 6(b). The reference, $T_{90,\text{ref}}$, and the estimate of T_{90} are also shown. The results

indicate that the temperature in the selected normal tissue location (which coincided with the location of the first thermocouple) is indeed constrained to below 7 °C during the course of the treatment. At the beginning of the treatment, the temperature inside the tumour reaches a maximum of 13.5 °C at the third thermocouple location before the controller automatically reduced the power to prevent the violation of normal tissue constraint, a reduction that brought the maximum temperature down to approximately 9.7 °C. As a result of a more stringent normal tissue constraint during the canine experiments (7 °C versus 10 °C in the phantom), the maximum temperature, reached in the canine tumour, is significantly lower than in the phantom. Consequently, in the canine patient the dose accrued during tissue cooling was relatively small. The faster cooling is the reason for selecting a shorter prediction horizon ($p = 7$) during canine experiments. Experiments to determine the effect of p and other tuning parameters on controller performance (results not included) confirmed the previously summarized tuning guidelines (Arora *et al* 2005a).

As evident from figure 6(c), the precise delivery of 20 CEM43° T_{90} is achieved in the tumour. Similarly to the phantom results, a sharp delineation of the delivered thermal dose between the tumour and the normal tissue is obtained, as can be seen in figure 7. On the pointwise basis, the maximum treatment dose of 110 CEM is delivered inside the tumour at the third thermocouple location.

4. Discussion

A control system for non-invasive thermal therapies that automatically executes physician-specified clinical efficacy and safety objectives is desirable but difficult to implement. Even the first step of translating clinical goals into achievable control objectives is non-trivial, with different solutions adopted for different treatment modalities, available power transducers, and depending on the expertise and experience of a research or clinical group.

A historically first approach to automatic control of treatment efficacy is by controlling temperature (usually, to a constant value) in one or several selected spatial locations. With noninvasive heating, it is generally impossible to obtain the desired temperature distribution in the target since pointwise temperature control requires a very large (theoretically infinite) number of manipulated variables. Nevertheless, control of temperature distribution can be improved with better transducers, SAR customization and more sophisticated treatment controllers. For instance, phased arrays with large number of elements greatly increase degrees of freedom available for automatic control, which improves the flexibility in achieving the desired temperature distribution (e.g., temperature uniformity) in geometrically complex and inhomogeneous targets. As an example of the benefits of an improved feedback control, Salomir *et al* (2000) were able to improve temperature uniformity with a single, scanned, focused ultrasound transducer by manipulating the scan velocity of the focal zone along a spiral trajectory.

For two common treatment modalities—hyperthermia and thermal ablation—the clinical efficacy is usually translated into different treatment control objectives. In hyperthermia, used as an adjuvant to chemo- and/or radiation therapies, the clinical goal is to, both, damage tumour cells directly, and to improve tissue perfusion and oxygenation (Dewhirst and Sneed 2003, van der Zee 2002). The treatment efficacy is then controlled by: (a) pre-treatment planning to select an appropriately large SAR pattern for a given geometry and properties of the target (Jarosz 1998), followed by (b) manually-triggered adjustments of the SAR pattern during the treatment. Conservative goal and relatively simple SAR adjustments needed to control the treatment are important reasons hyperthermia is the only noninvasive thermal treatment in routine clinical use (van der Zee *et al* 2004).

The clinical goal of noninvasive thermal ablation is to cause tissue necrosis inside the target. This is often achieved with a pulsed application of high-intensity energy, sequentially focused in distinct spatial locations (Hynynen *et al* 2001, Huber *et al* 2001), or along a continuous scan trajectory (Palussiere *et al* 2003). For example, using focused ultrasound, ablation may be controlled by: (1) treatment planning to select the sequence of spatial locations of focal zones and durations each location is sonicated to cause tissue necrosis; (2) execution of pre-optimized treatment protocol.

The issue of thermal safety of the normal tissue is less pronounced in hyperthermia since low temperature elevations (usually, below 43 °C) are induced. On the other hand, safety of high-intensity treatments is an important consideration. In the traditional approach to HIFU treatments, efficacy and safety objectives are implicitly decoupled by using highly focused transducers, which limits intense heating to a small focal zone, and by pulsed application of ultrasound power, consisting of power-on/power-off cycles. During power off, the normal tissue temperature decays and approaches the equilibrium value. Therefore, treatment safety can be assured by adjusting the power-off duration, which limits normal tissue temperatures by intermittent cooling. The pulsed, focused treatment also simplifies control of efficacy. With long power-off periods, the thermal buildup (McDannold *et al* 1999) caused by prior pulses dissipates, and the sequential positions may be treated independently.

Treatment safety and efficacy are competing objectives, and must be implicitly or explicitly balanced. This paper describes the first implementation of a control system which achieves such balance explicitly and automatically. Several innovations made such a system possible:

- a. *Feedback control of the thermal dose.* In our approach, a thermal dose is used to quantify the treatment efficacy. Tissue ablation can be achieved by delivering thermal dose equal or exceeding 240 CEM (Chung *et al* 1999). In the case of hyperthermia, the goal is to deliver a relatively low thermal dose (typically 10–100 CEM) (Maguire *et al* 2001). Though it was recognized before that TD control is a promising approach to thermal treatments (e.g., McDannold and Jolesz 2000), the direct, automatic control of the thermal dose proved difficult to achieve because of the presence of strongly nonlinear and integrating dose-temperature relationship (equation (1) or (3)). The solution described in this paper is the treatment control system with cascade structure. It consists of the main, nonlinear thermal dose controller K_D , which dynamically updates the reference temperature trajectory for the secondary temperature controller K_T , used to manipulate the applied ultrasound power.
- b. *Constrained control of thermal treatments.* The designed controller automatically delivers the specified thermal dose without violating safety constraints. The safety is specified in terms of peak allowable temperatures (equation (13)) in the selected normal tissue locations.
- c. *The trade-off between treatment efficacy and safety is optimized in real time.* The developed treatment controller dynamically solves the constrained optimization problem (12), which is a formal expression of efficacy and safety objectives. The systematic handling of treatment constraints removes the need for pulsed application of ultrasound power. Instead, the ultrasound power is automatically adjusted to satisfy safety constraints. The treatment may now be shortened by eliminating unnecessary tissue cooling, and exploiting thermal buildup inside the target caused by the interaction of power inputs. The developed approach allows a physician to explicitly specify safety constraints, which the treatment controller automatically complies with. Note, however, that more stringent safety specifications lead to longer treatments or even an infeasible control problem. In

either case, on-line treatment optimization allows a physician to dynamically modify safety and efficacy specifications, as necessary to avoid infeasibility or excessive length of a treatment. Constraints on maximum transducer power can also be imposed (equation (14)) to reflect hardware limitations and to avoid tissue cavitation (Hynynen 1991).

- d. *The developed controller is model-based and model-predictive.* This property allows the treatment control system to assess the effect and interaction of m control actions over p steps into the future ($p - m$). The estimation of the residual thermal dose delivered during tissue cooling also becomes possible, and can be taken into account to minimize the active treatment time. In our implementation, the predictive model used in the controller is constantly updated to reduce errors between predicted and measured temperatures, acquired during the treatment. The model adaptation is an important feature for at least two reasons. First, accurate models are difficult to identify and computationally expensive to use during real time operation. Changing blood perfusion, thermal conductivity and ultrasound absorption of the target is the second reason the dynamic model adaptation is needed, since an initially accurate model will not reflect *a priori* unknown changes during the treatment.

The proposed approach to thermal treatment control is relevant to a broad range of therapies. In this paper, this approach is evaluated *in vivo* and in phantoms for the case of a single, focused ultrasound transducer with fixed focal zone. The results demonstrate an accurate delivery of the specified thermal dose to the target without violating user-defined safety constraints. The experiments provide further indication that the developed controller can be tuned to achieve the minimum-time treatment—a clinically desirable feature. The observed controller performance as a function of tuning parameters (Δt , m , p , and weights in objective function J) is qualitatively similar to previous simulation results (Arora *et al* 2005a).

The extension of the developed approach to different thermal treatments is straightforward in some cases, and will require a substantial effort in others. Without any modifications, the described system can be used to control safety and efficacy of hyperthermia and thermal ablation for the targets treatable with a fixed SAR. The case of time varying SAR pattern, created by mechanical scanning or electronic steering, is more difficult to implement, and is the subject of our current research. As an illustrative example, consider thermal ablation of large tumours using focused ultrasound. The simplest adaptation of the proposed approach will involve a subdivision of the tumour into subregions, determined by the size and shape of focal zone, and their sequential treatment to the desired thermal dose, controlled by the described system. The sequence of subregions can be obtained as a result of pre-treatment optimization, or by following the selected focal zone trajectory (e.g., rastering, Wan *et al* 1996). The treatment interaction in different subregions can be accounted for by adapting the thermal dose setpoint to reflect the already delivered dose due to SAR overlap and heat transfer. During the entire treatment, the controller will automatically adjust the power to ensure that normal tissue constraints are not violated, no matter the location of the focal zone. A more advanced implementation will require the development of a control system to automatically manipulate the focal zone location, rather than relying on pre-specified sequence of positions or trajectories, selected before the treatment.

Accurate and frequent temperature measurements are required in the feedback of the developed treatment control system. This is especially true in the case of HIFU treatments, which may take 20 s or less to treat a subregion. The canine and phantom experiments, described in this paper, used pointwise thermocouple measurements, which are, both, accurate and can be sampled at a high rate. However, the developed control system can also

utilize noninvasive magnetic resonance (MR) thermometry, as validated *in vivo* (Arora *et al* 2005b) using MR temperature feedback, sampled less frequently (every 3 s), and affected by the measurement noise in the range of ± 0.5 °C.

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Figure 1. Feedback control of the thermal dose. K_D : dose controller; K_T : temperature controller; P : Patient; E : temperature estimator; $S(\cdot)$: T_{90} selector; H : dose estimator.

Figure 2.
Thermal treatment control system during *in vivo* experiments.

Figure 3. Results of the pre-treatment parameter identification for agar phantom and canine patient: Power deposition pattern, $Q(x)$ (left), and effective perfusion, $W_e(x)$.

Figure 4.

Thermal dose control in agar phantom. The desired CEM43° T_{90} was set to 30 min. The maximum allowable temperature increase in the specified location ($x = 0.6$ cm) inside the normal tissue was set to 10 °C. The results are for the moving treatment horizon $\Delta t = 10$, prediction horizon $p = 10$, and the control horizon $m = 5$. (a) Control input (applied ultrasound power). (b) Increase in all measured temperatures, T_{90} , $T_{90,ref}$ and T_{cons} . (c) Delivered thermal dose (CEM43° T_{90}).

Figure 5.
Thermal dose distribution along the length of the thermocouple array inside agar phantom.
Thermocouples 4 through 6 are inside the tumour.

Figure 6.

Thermal dose control in *in vivo* canine muscle. The desired CEM43° T_{90} is set to 20 min. The maximum allowable temperature increase in the specified location ($x = 1.6$ cm) inside the normal tissue is 7 °C. The results are obtained with the moving treatment horizon $\Delta t = 7$, prediction horizon $p = 7$ and the control horizon $m = 1$. (a) Control input. (b) Increase in all measured temperatures, T_{90} , $T_{90,ref}$ and T_{cons} . (c) Thermal dose.

Figure 7.
Thermal dose distribution along the length of the thermocouple array inside canine muscle.
Thermocouples 2 and 3 are inside the tumour.