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Minimum-Time Thermal Dose Control of Thermal Therapies

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Abstract

The problem of controlling noninvasive thermal therapies is formulated as the problem of directly controlling thermal dose of the target. To limit the damage to the surrounding normal tissue, the constraints on the peak allowable temperatures in the selected spacial locations are imposed. The developed controller has a cascade structure with a linear, constrained, model predictive temperature controller in the secondary loop. The temperature controller manipulates the intensity of the ultrasound transducer with saturation constraints, which noninvasively heats the spatially distributed target. The main nonlinear thermal dose controller dynamically generates the reference temperature trajectories for the temperature controller. The thermal dose controller is designed to force the treatment progression at either the actuation or temperature constraints, which is required to minimize the treatment time. The developed controller is applicable to high and low-intensity treatments, such as thermal ablation and thermoradiotherapy. The developed approach is tested using computer simulations for a one-dimensional model of a tumor with constraints on the maximum allowable temperature in the normal tissue and a constrained power output of the ultrasound transducer. The simulation results demonstrate that the proposed approach is effective at delivering the desired thermal dose in a near minimum time without violating constraints on the maximum allowable temperature in healthy tissue, despite significant plant-model mismatch introduced during numerical simulation. The results of *in vitro* and *in vivo* validation are reported elsewhere.

Index Terms

Minimum-time control; thermal dose control; thermal therapies

I. Introduction

Thermal therapies involve the use of elevated temperatures for therapeutic applications. Dewhurst and Sneed [1] summarized seven Phase III trials that showed a positive effect of low-intensity thermal therapies in combination with radiation treatments for different cancer types and sites. Van der Zee and Hulshof [2] quote 18 randomized studies that showed positive effect of thermal therapies used in combination with radiotherapy (13 studies), chemotherapy (3 studies), or the combination of thermal, radio- and chemotherapies (2 studies). Similarly, the feasibility of high-intensity thermal therapies (such as thermal surgery including high-intensity focused ultrasound therapy) to noninvasively coagulate/ablate spatially distributed targets inside the patient has been demonstrated in several

studies. For instance, Hynynen *et al.* [3] used high temperature (up to 90 °C) MR-guided ultrasound surgery to noninvasively coagulate benign breast fibroadenomas.

The concept of the thermal dose (TD) has been used to quantify the relationship between treatment efficacy and the target temperature as a function of time. It is generally agreed that the effectiveness of thermal treatments depends on the cumulative effect of elevated temperatures $T(t)$ over the treatment time. Therefore, in the most general form, the pointwise thermal dose can be defined as

$$D(t;x,y,z)=\int_0^t f(T(\tau;x,y,z),\tau)d\tau. \quad (1)$$

If the temperature distribution inside the target is characterized by its percentile value(s), or moment(s) (such as a median), then a single thermal dose can be assigned to the entire target, resulting in the simplified expression

$$D(t)=\int_0^t f(T_c(\tau),\tau)d\tau \quad (2)$$

where T_c is the selected characterization of the temperature distribution.

Different expressions for the integrand $f(\cdot)$ in (1) and (2) have been previously proposed and used to characterize the treatment efficacy. Sapareto and Dewey [4], based on extensive experimental results with cell culture, proposed to convert the treatment time δt , when the tissue is maintained at a uniform $T^\circ\text{C}$, to an equivalent time Δt_{eq} at temperature T_{eq} (usually 43 °C) using

$$\Delta t_{eq}=\delta t R^{(T_{eq}-T)} \quad (3)$$

where the empirical constant R [5] is given by

$$R=\begin{cases} 0, & \text{for } T<39^\circ\text{C} \\ 0.25, & \text{for } 39<T<43^\circ\text{C} \\ 0.5, & \text{for } T>43^\circ\text{C} \end{cases} \quad (4)$$

One commonly used definition of the thermal dose is based on the number of the cumulative equivalent minutes at 43°C (CEM43 °C), which defines f in (1) as

$$f(T(t;x,y,z),t)=R^{[43-T(t;x,y,z)]}. \quad (5)$$

An alternative expression for the thermal dose is based on T_{90} , the 10th percentile of the measured temperatures¹, which according to the clinical study of Leopold *et al.* [6] can be adequately used to characterize the treatment efficacy. The thermal dose based on T_{90} (CEM43° T_{90}) is defined using

$$f(T_c(t),t)=R^{[43-T_{90}(t)]}. \quad (6)$$

¹90% of all measured temperatures in the spatially distributed target are higher than T_{90}

This last definition is used in multiple studies (see, for example, [7], [8]), and is adopted in this paper. Other definitions of the thermal dose based on different percentiles and moments of the temperature distributions have also been proposed [1].

Multiple definitions of the thermal dose indicate that the question of an adequate characterization of the efficacy of thermal treatments is not entirely resolved. In fact, a recent clinical Phase II study [7] indicates that the most commonly used definition of the thermal dose, $\text{CEM43}^\circ T_{90}$, does not correlate well with the treatment efficacy. Specifically, the study shows that with $\text{CEM43}^\circ T_{90}$ as the efficacy measure, the achieved pCR (pathological complete response) is less than 75% in high-grade soft tissue sarcomas treated with thermoradiotherapy.

Despite the lack of the uniform acceptance of a single definition of the thermal dose, the general expressions (1) and (2) indicate that a thermal dose is a nonlinear integrator [9] of temperatures, and the control of the thermal dose is characterized by several distinguishing features irrespective of the selected expression for the integrand f .

1. The absolute value of the dose is a nondecreasing, bounded variation function [10]. More specifically $D(t_1) \leq D(t_2)$ whenever $t_1 \leq t_2$, reflecting the fact that the delivered dose cannot be reduced.
2. The system describing the dose delivery process is an example of a system with an aftereffect [11]. Indeed, when the actuation is switched off and the temperature of the target tends to its equilibrium values of 37°C , the thermal dose continues to increase as long as the temperature remains elevated.²

The subject of this paper is the control of the thermal dose in thermal treatments, including low and high intensity therapies. The direct control of the thermal dose is particularly important in the case of high-intensity, high temperature therapies, during which large temporal temperature fluctuations are common. The principal reasons why the effective feedback control of thermal treatments is essential include treatment disturbances, errors in thermal and power deposition models used during pre-treatment planning and optimization, and the need to limit damage to the normal tissue surrounding the tumor.

All previous research efforts (e.g., [12], [13]) concentrated on controlling *temperatures* in several spatial locations, which is largely a reflection of the difficulty of directly controlling thermal dose because of the highly nonlinear and integrating relationship between the dose and the temperatures. One exception is our previous work on low-intensity treatments [14], [15], where the direct control of the thermal dose was achieved using continuous linearization of the dose-temperature relationship.

We formulate the problem of controlling thermal treatments as a problem of delivering the prescribed thermal dose, defined as $\text{CEM43}^\circ\text{C}$ based on $T_{90}(t)$. The $\text{CEM43}^\circ T_{90}$ dose has the same distinguishing features as the thermal dose in the most general definition. With minor modifications, the approach developed in this paper can be used to control the delivery of an alternatively defined thermal dose. The proposed approach is equally applicable to low-intensity treatments (e.g., combination therapies, such as hyperthermia + radiation) where the goal is usually to deliver $10 \text{ CEM43}^\circ T_{90}$ [7], and thermal surgeries, which typically require a higher dose of $240 \text{ CEM43}^\circ\text{C}$ [16]. Unlike the results of the previous work [14], [15], the approach developed in this paper does not require linearization of the dose-temperature relationship, which makes it applicable to the control of high intensity treatments.

²According to the thermal dose definition (2) and (5), or (6), a nonzero thermal dose is delivered whenever $T > 39^\circ\text{C}$

The developed controller has a cascade structure with the secondary temperature control loop receiving the reference trajectory from the outer thermal dose controller. The temperature controller is implemented as a linear, constrained, model-predictive controller (MPC), which ensures that the constraints on the maximum allowable temperature in the healthy tissue are satisfied, while dynamically minimizing the weighted 2-norm of the error between the actual and the desired temperature trajectories. The nonlinear thermal dose controller dynamically updates a reference trajectory for the temperature controller based on the difference between the desired final thermal dose and the already delivered dose.

The thermal dose controller is designed to minimize the treatment time without directly solving the minimum time problem. Simulations using a one-dimensional (1-D) model of a tumor with constraints on the maximum allowable temperature in normal tissues are performed to test the robustness and effectiveness of the proposed approach. The computer simulations show that a close to minimum treatment time for delivering the desired thermal dose is achieved despite plant-model mismatch, and without exceeding the maximum allowable temperature in the normal tissue. The results of *in vitro* and *in vivo* validation of the proposed approach are reported in [17]–[19].

II. Problem Description

A. Control Problem

The following control problem is posed: Achieve the desired final thermal dose, D_f in the tumor using noninvasive ultrasound power deposition. It is assumed that temperature measurements are available at a limited number of pointwise spatial locations, obtained using catheterized sensors, or localized magnetic resonance (MR) temperature measurements. Note that MR thermal images may be viewed as a collection of a large number of pointwise temperature measurements. To minimize side effects of the treatment, the maximum allowable temperature constraints may be imposed on the temperatures in normal tissues surrounding the tumor. The maximum power of the ultrasound transducer is constrained to prevent cavitation in tissue, and to account for hardware limitations. Furthermore, it is desirable to minimize the overall treatment time, t_f without violating the imposed temperature constraints.

B. Treatment Model

1) Thermal Model of the Tissue—Thermal energy transport in the tissue is traditionally modeled using the following semi-empirical model known as the Pennes' bioheat transfer equation [20]

$$\rho C \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - W_b C_b (T - T_a) + Q \quad (7)$$

where C and C_b are specific heat of tissue and blood [J/(kg°C)], W_b [kg/(m³s)] is a blood perfusion related parameter [21] T_a is the arterial temperature (assumed to be 37°C), and Q [W/m³] is the power deposited in the tissue. Predictions of this equation have shown good agreement with experiments in previous studies [22]–[27].

The performance of the control system of the thermal treatment is evaluated using a 1-D tissue model shown in Fig. 1, which preserves the most important features of the problem, including the spatial inhomogeneity and distributed nature of the target. The inhomogeneous tissue is modeled as a tumor surrounded by muscle layers on either side. In the 1-D case of Fig. 1, (7) is reduced to

$$\rho C \frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2} - W_b C_b (T - T_a) + Q \quad (8)$$

where constant conductivity is assumed, and $x \in [0, 13]$ is the depth into the tissue. It is further assumed that $T = T_a$ at both the skin surface ($x = 0$) and $x = 13$. Thermal and acoustic properties of each region are summarized in Table I.

2) Actuator Model—A single, focused ultrasound transducer with fixed characteristics is assumed. The spatial location of the transducer relative to the patient is assumed to be fixed during pre-treatment planning. These assumptions simplify the implementation of the controller and the analysis of its performance, but retain the essential features of the practical problem of controlling thermal treatments in a clinically common configuration. The controller developed in this paper can be modified to allow for moving and phased-array transducers.

With the above assumptions, the power deposition term $Q(x)$ represents the energy deposited by a focused ultrasound transducer. In the 1-D case, the energy deposition (W/m^3) along the centerline of the transducer's ultrasound field is equal to [30]

$$Q(x) = 2\alpha_i I(0) \left[\frac{r}{r-x} \sin \left(\frac{\pi d^2 (r-x)}{8\lambda x r} \right) \right]^2 e^{-\sum \alpha_i S_i} \quad (9)$$

where $I(0)$ is the average intensity over the radiating surface d , is the diameter of the transducer, r is the radius of curvature and x is the distance along the centerline from the transducer. α_i and S_i are attenuation coefficient and penetration length for layer i , respectively. Fig. 2 shows the power deposition, $Q(x)$, inside the tissue, for a transducer with $r = 25\text{cm}$, $d = 70\text{mm}$, $\lambda = 1\text{mm}$ and $I(0) = 8,000 \text{ W/m}^2$, which is used in the subsequent 1-D simulation study. The transducer is positioned at $x = -17$, or 17 cm away from the skin. With these assumptions, the focal point is at $x \approx 5 \text{ cm}$.

3) State Space Formulation—After finite dimensional approximation, the bioheat transfer model (8) is expressed in the state-space form:

$$\dot{\mathbf{T}} = \mathbf{A}\mathbf{T} + \mathbf{B}u \quad (10)$$

$$T_{90} = \mathcal{S}(\mathbf{T}) \quad (11)$$

where $\mathbf{A}$ is the system matrix incorporating both conduction and perfusion terms and $\mathbf{B}$ is the input matrix determined by (9). For the 1-D case, the state $\mathbf{T}$ is a vector of temperature elevations above T_a in 131 mesh nodes of the tissue model and u is $I(0)$, a single manipulated variable. In the output equation (11), the operator $\mathcal{S}(\mathbf{T})$ selects the T_{90} temperature.

III. Dose Controller

The thermal dose control problem is characterized by several distinguishing features:

1. It is typically required to limit damage to the normal tissue, and to minimize the patient's pain and discomfort. The most natural expression of this requirement is to impose an upper constraint on the dose delivered to the normal tissue. However, constraints in such a formulation depend on *future* temperatures (noncausal

constraints), thus leading to a noncausal dose controller, which is undesirable. To avoid noncausal formulation, we adopt an alternative approach of constraining the maximum allowable temperature in the normal tissue.

2. It is typically desirable to minimize the treatment time, which requires an aggressive controller. Though the closed-loop stability with an aggressive controller is not a concern in this case (the system is dissipative, returning to pretreatment thermal equilibrium after the actuation is switched off when the desired thermal dose is reached), it is difficult to avoid target overdosing in systems with aftereffect.
3. Model predictive control is an attractive approach to the control of the dose delivery problem because it directly accounts for actuation and state constraints, and, with an adequately long prediction horizon, the system aftereffects can be accounted for. However, a strongly nonlinear relationship between temperature and thermal dose limits the application of linear MPC methods. Furthermore, a significant plant-model mismatch should be expected: An accurate patient- and site-specific model of the treatment is difficult to develop, and the process is known to change during treatment. For example, the target may move or swell, or blood perfusion may increase significantly in response to the elevated temperature [31], which strongly influences temperature distribution in the target, as well as in the healthy tissue.

Our earlier work [14], [15] utilized direct model-predictive thermal dose control with piecewise linearization of the thermal dose relation (2), (6), which limits its application to the case of relatively low temperature treatments. In particular, our first generation thermal dose controller is inadequate for poorly perfused tumors and high intensity, short duration therapies. In this paper, the problem of controlling noninvasive thermal therapies is formulated as the problem of directly controlling thermal dose without linearization.

Under the highly idealized assumptions of no plant-model mismatch, unperturbed treatment, and no effect of the thermal dose on the ultrasound power deposition and tissue heat transport, the thermal dose controller may be implemented as a feed-forward controller (e.g., [32]). However, to achieve an effective control of thermal treatments under realistic conditions, the feedback thermal dose controller is required.

The feedback thermal dose controller, as proposed in this paper, is computationally efficient and results in a close to time-optimal treatment strategy. The developed controller may be viewed as inherently self-optimizing in the sense that it possesses structural properties which yield near time-minimal control without explicit on-line solution of the corresponding state and input constrained nonlinear optimal control problem.

A. Problem Statement

The thermal dose control problem is formulated as a problem of finding a controller K_D , which maps the desired final thermal dose D_f into the temperature trajectory $T(t)$

$$K_D: D_f \rightarrow T(t, u(t)) = T_{\text{ref}}(t), \quad t \in [0, t_f] \quad (12)$$

such that $D[T(t, u(t))] \rightarrow D_f$ as $t \rightarrow t_f$. The role of the temperature controller is to track the reference trajectory while satisfying state and actuator constraints

$$u \in U(\text{e.g., } 0 \leq u(t) \leq u_{\max})$$

$$T \in \mathcal{T}(\text{e.g., } T \text{ in normal tissue} \leq T_{\text{peak}}).$$

Several implementation alternatives of K_D are discussed below. We start by considering different options for implementing K_D as a feedforward controller depicted in Fig. 3, where the temperature controller K_T tracks the K_D -generated reference temperature trajectory. Once the properties and limitations of the feedforward implementation are understood, the feedback thermal dose controller is proposed with the structural property that allows it to achieve near time-optimal solution without explicit on-line optimization. The simulation study is then used to investigate the performance of the controller under different assumptions.

B. Feedforward Control of the Thermal Dose

Ideally, a map (12) should be generated for each spatial location of the target, followed by the temperature control to its reference value. However, the existing power deposition transducers, such as the focused ultrasound transducer described in Section II-B2, do not allow for an arbitrary power deposition pattern needed for pointwise control of complete temperature distribution in the targets. The introduction of a reduced number of controlled variables, such as a temperature, can be used to circumvent the underactuated nature of the temperature control problem. Since T_{90} has been shown to be an effective measure of treatment efficacy, we modify the general problem (12), and design the dose controller K_D to map the desired final thermal dose into the T_{90} temperature trajectory

$$K_D: D_f \rightarrow T_{90,\text{ref}}(t), t \in [0, t_f]. \quad (13)$$

The map (13) may be implemented as

$$K_D[D_f] = \mathcal{M}_2[\mathcal{M}_1(D_f)] = T_{90,\text{ref}}(t) \quad (14)$$

where $\mathcal{M}_1: D_f \rightarrow D_{\text{ref}}(t)$ and $\mathcal{M}_2: D_{\text{ref}}(t) \rightarrow T_{90,\text{ref}}(t)$, $t \in [0, t_f]$ are inverse operators. To ensure the uniqueness of mapping (13), additional conditions must be imposed. Such conditions may include the requirement that the map is optimal in some appropriate sense (e.g., minimum-time solution), or the uniqueness can be obtained by parameterizing the reference temperature (explicit parameterization) or the thermal dose (implicit parameterization) trajectories. Past experience and heuristic rules can also be used to obtain the reference temperature trajectory. Note that t_f is generally unknown *a priori*.

In the case of *explicit parameterization*, $\mathcal{M}_1$ is the identity operator. The reference temperature trajectory is expressed using the selected functional form $\mathcal{P}_e(\varphi_e, t)$, parameterized with a vector φ_e found from

$$\mathcal{M}_2^{-1}: T_{90,\text{ref}}(t) = \mathcal{P}_e(\varphi_e, t | t \in [0, t_f]) \rightarrow D_{\text{ref}}(t_f) = D_f. \quad (15)$$

In the case of thermal treatments with the adopted definition of the thermal dose, the map $\mathcal{M}_2^{-1}$ is governed by (2) with given by (6). The simplest explicit parameterization is $T_{\text{ref}}(t) = \varphi = \text{const}$, which leads to the goal of standard hyperthermia [33] of maintaining a constant temperature during the entire treatment.

The *implicit parameterization* of the reference temperatures starts with the parameterization of the reference dose trajectory $D_{\text{ref}}(t) = \mathcal{P}_i(\varphi_i, t)$, where the parameterization vector φ_i is selected to satisfy the following equation:

$$\mathcal{M}_1: D_f \rightarrow D_{\text{ref}}(t) = \mathcal{P}_i(\varphi_i, t) \text{ such that } \mathcal{P}_i(\varphi_i, t_f) = D_f. \quad (16)$$

For example, linear, exponential, and Gompertz [34] dose parameterization are given by the following expressions, respectively

$$\mathcal{P}_{i1}(\alpha, t): D_{\text{ref}}(t) = D(0) + \alpha t, \quad \alpha = \frac{D_f - D(0)}{t_f}, \quad \varphi_i = \alpha \quad (17)$$

$$\mathcal{P}_{i2}(\tau, t): D_{\text{ref}}(t) = D_f(1 - e^{-t/\tau}), \quad \varphi_i = \tau \quad (18)$$

$$\mathcal{P}_{i3}(k, a, t): D_{\text{ref}}(t) = D(0) \exp \left[\frac{k}{a}(1 - e^{at}) \right], \quad \varphi_i = \begin{bmatrix} k \\ a \end{bmatrix}. \quad (19)$$

With the selected parameterization, the reference trajectory for T_{90} is found from

$$\mathcal{M}_2: \mathcal{P}_i(t) \rightarrow T_{90, \text{ref}} \quad (20)$$

where $\mathcal{M}_2$ is the solution of the following equation:

$$\frac{d\mathcal{P}_i(t)}{dt} = \frac{R^{43}}{R^{T_{90, \text{ref}}(t)}} \quad (21)$$

obtained by differentiating expression (2) with f defined by (6). Note that the implicit parameterization $\mathcal{P}_{i3}$ is equivalent to the explicit parameterization $T_{\text{ref}} = \text{const}$.

The simulation results for the feedforward control of the thermal dose with three different parameterizations (17)–(19) are depicted in Fig. 4. All simulations use deviation temperature from thermal equilibrium $T_a = 37^\circ\text{C}$. The simplest case of a “single-point” target is assumed, which often is an adequate model for small tumors. In the single-point case, the target temperature and T_{90} are equal. The temperature controller K_T is implemented as an unconstrained model predictive controller. Both linear and exponential parameterizations of the thermal dose require an instantaneous increase in the target temperature at the beginning of the treatment, which is not realizable. The linear parameterization also requires an instantaneous decrease of the target temperature toward the end of the treatment. $\mathcal{P}_{i2}$ leads to a linear decrease of $T_{90, \text{ref}}$, which could be more closely followed by the K_T controller. The Gompertz-parameterized thermal dose leads to the reference temperature trajectory, which could be closely followed, but the treatment time is now very long. Note that small errors in tracking high reference temperature may lead to significant errors in the delivered thermal dose at the end of the treatment.

To ensure that the reference temperature is feasible, the dynamic properties of the process should be explicitly taken into the account, requiring model-based parameterization of the map (13). An alternative is to use a slowly changing reference temperature, which, however, leads to long treatment times.

C. Feedback Control of the Thermal Dose

The feedforward control of the thermal dose selected as the solution of the optimal control problem, or as an inverse problem with model-based parameterization, is sensitive to plant-model mismatch and process disturbances unavoidable during thermal treatments. Therefore, faithfully tracking the reference generated by feedforward K_D based on an erroneous model makes little sense. If $T_{\text{ref}}(t)$ is generated as the optimal solution in some suitable sense, then dynamic recalculation of the optimal reference temperature trajectory to account for available measurements will lead to a nonlinear MPC approach to thermal-dose control, which is computationally expensive. Other problems related to on-line calculation of the nonlinear optimal control include potential infeasibility of the solution, and failure to converge in deterministic time.

An alternative approach of implementing K_D as an inversion based feedback controller is adopted in this paper. The proposed K_D is designed to be a structurally self-optimizing controller, which generates a near time-optimal solution of the dose delivery problem *without explicit on-line solution* of the minimum-time problem.

K_D is designed to map the difference between the desired and current thermal dose into the temperature trajectory

$$K_D: [D_f - D(t_k)] \rightarrow T_{90,\text{ref}}(t), t \in [t_k, t_f] \quad (22)$$

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. The map (22) can be implemented as

$$K_D [D_f - D(t_k)] = \mathcal{M}_2 [\mathcal{M}_1 (D_f - D(t_k))] = T_{90,\text{ref}}(t) \quad (23)$$

where $\mathcal{M}_1: [D_f - D(t_k)] \rightarrow D_{\text{ref}}(t)$ and $\mathcal{M}_2: D_{\text{ref}}(t) \rightarrow T_{90,\text{ref}}(t)$ are inverse operators. To ensure the uniqueness of the map $\mathcal{M}_1$, the reference thermal dose is expressed using a selected functional form $\mathcal{P}$, parameterized with a vector ϕ . Then for every t_k

$$\mathcal{M}_1: [D_f - D(t_k)] \rightarrow \phi, D_{\text{ref}}(t) = \mathcal{P}(\phi, t). \quad (24)$$

Turning our attention to the problem of selecting parameterization $\mathcal{P}$, we first note that it follows from the Pontryagin's maximum principle [35] that the *minimum treatment time is achieved when either power or/and temperature constraints are active*. Therefore, to minimize the treatment time, at the beginning of the treatment when $D_{\text{ref}} - D(t_k)$ is large, the particular form of parameterizations $\mathcal{P}$ is not important as long as the reference temperature trajectory is aggressive enough to force the activation of the power or temperature constraints. As $D(t_k)$ approaches D_f to prevent the overshoot in the delivered thermal dose, the reference $D_{\text{ref}}(t)$ must become less aggressive so that the corresponding $T_{90,\text{ref}}(t)$ is an attainable trajectory. One possible $\mathcal{P}(\phi, t)$ with the desired properties is given by the implicit parameterization $\mathcal{P}_{i1}$

$$D_{\text{ref}}(t) = D(t_k) + \alpha(t_k)[t - t_k]. \quad (25)$$

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

$$\alpha(t_k) = \frac{(D_f - D(t_k))}{(t_f - t_k)} \quad (26)$$

$$t_f = t_k + \Delta t \quad (27)$$

where Δt is the tuning parameter, referred to as *moving treatment horizon*. The subsequent simulation results show the effect of Δt on the performance of K_D .

The alternative interpretation of (25) is obtained by noting that $\mathcal{P}_a$ is equivalent to the explicit parameterization $T_{90,\text{ref}}(t) = \text{const}$, $t \in [t_k, t_f]$. From this perspective K_D continuously recalculates a constant temperature setpoint, which, if maintained over $[t_k, t_k + \Delta t]$, leads to the delivery of the remaining thermal dose $D_f - D(t_k)$.

The parameterization (25) may be viewed as linear approximation of the optimal trajectory for $D_{\text{ref}}^*(t)$, defined by

$$\mathcal{M}_2^{-1}: T_{90,\text{ref}}^*(t) \rightarrow D_{\text{ref}}^*(t), \quad t \in [t_k, t_f] \quad (28)$$

where the optimal temperature trajectory $T_{90,\text{ref}}^*(t)$ may be calculated from the solution of the minimum-time problem. Note that in our implementation of the dose controller, the explicit calculation of the time-optimal solution is not necessary.

With the obtained $D_{\text{ref}}(t)$, $\mathcal{M}_2$ is simply the inverse of the integral (2) with f defined by (6), resulting in the following reference trajectory:

$$T_{90,\text{ref}}(t) = \frac{1}{\ln\left(\frac{1}{R}\right)} \ln \frac{\alpha(t_k)}{R^{43}}, \quad t \in [t_k, t_k + \Delta t]. \quad (29)$$

$T_{90,\text{ref}}(t)$ is updated each time the next thermal dose estimation becomes available.

The selection of $D_{\text{ref}}(t)$ according to (25) with a small tuning parameter Δt forces the activation of power and/or temperature constraints when $D_f - D(t_k)$ is large. Toward the end of the treatment, the slope α flattens, resulting in a more attainable reference trajectory $T_{90,\text{ref}}$.

The deviation from time optimality of the proposed approach is caused by the difference in the way the thermal dose is delivered to the patient at the end of the treatment. In the minimum-time solution, the residual thermal dose is delivered during the tissue cooling with the power switched off. The temperature decay during cooling is close to exponential, and its piecewise constant approximation according to (29) will generally lead to small but nonzero power input with none of the constraints active.

The overall structure of the thermal dose control system is depicted in Fig. 5. At time t_k , the temperatures $T_{\text{mea}}(k)$, measured in a limited number of spatial locations inside the patient, P , are used in a Kalman filter, E , to estimate the temperature distribution for the entire spatial area of interest. The estimated temperature distribution, $T_A(k)$, 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 temperature control loop. Block H is used to estimate, according to (2) and (6), the thermal dose, D , delivered to the patient up to the current time t_k . D is used as a feedback 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 $T_{90,\text{ref}}(t), t \in [t_k, t_f]$ using parameterization $\mathcal{P}_u$, (29).

The secondary temperature controller K_T is implemented as the linear, constrained, model predictive controller, which generates control u as a solution of the optimization problem

$$\min_u J(k) = \sum_{j=1}^p w_y(j) [T_{90,\text{ref}}(k+j) - T_{90}(k+j)]^2 + \sum_{j=1}^m w_u(j) [u(k+j-1)]^2 \quad (30)$$

subject to the equality constraints in the form of the predictive model (10)–(11), and the following inequality constraints:

$$T_n(k+j) \leq T_{n,\text{max}} \quad j \in [1, p] \quad (31)$$

$$0 \leq u(k+j-1) \leq u_{\text{max}} \quad j \in [1, m]. \quad (32)$$

Here, w_y is the weight on the quadratic error between the desired and the predicted T_{90} , w_u weighs the control effort, p and m are prediction and control horizons, $T_{n,\text{max}}$ is the maximum allowable temperature in the normal tissue and u_{max} is the transducer saturation limit. In our design, the control penalty is typically set to zero (and $w_y(j)=1$), which reflects the objective of achieving near time-optimal solution. To avoid infeasibility of the temperature control problem, the constraints on the maximum allowable temperature in normal tissue are implemented as soft constraints: When satisfied, soft constraints have no effect on the objective function; when violated, a large penalty is imposed on the value of J .

IV. Simulation Results

The performance of the controller is tested on a simulated nonlinear plant, represented as a combination of a simulated patient P (Fig. 5) with the nonlinear dose model H given by (2) and (6). Assuming a limited number of pointwise temperature measurements provided by catheterized sensors and/or MR thermometry, the estimation of the temperature distribution in the tumor and normal tissue is obtained using the Kalman filter, Block E , Fig. 5. For the 1-D case depicted in Fig. 1, the temperature profile is estimated assuming pointwise temperature measurements in 18 spatial locations: 2 in the muscle before the tumor, 9 in the tumor and 7 in the muscle after the tumor. The assumed number of measurements is larger than in a typical clinical application with catheterized thermocouples, but is substantially smaller than achievable with MR thermal imaging. The sampling rate of 1 s is selected to match currently achievable sampling rate with the MRI thermometry [36], [37].

The maximum allowed transducer intensity is fixed at $u_{\text{max}} = 6 \times 10^3 \text{ W/m}^2$, selected to mimic high-intensity, short-duration thermal treatments, such as high-intensity focused ultrasound (HIFU) therapy. The previously designed thermal dose controller [14] provides satisfactory performance only for low-temperature therapies, and is inadequate for high-intensity, HIFU-type treatments. Compared to [14], [15], we do not assume that the power is applied in a pulsed form. The pulsed application of energy was thought to be necessary to prevent damage to the normal tissue by allowing it to cool during power-off intervals. With the direct incorporation of the temperature constraints into the design of the thermal dose controller, the pulsed-power is no longer required. The nominal blood perfusion is set to $5 \text{ kg/m}^3 \text{ s}$. A substantial mismatch between the nominal and the actual perfusion is later introduced in the simulations (Sections IV-B and IV-C) to test the controller performance with large modeling errors, which may be present in clinical applications. The desired dose

is set to $240 \text{ CEM43}^\circ T_{90}$ (similar to the dose objective during thermal ablation [16]) for all the simulations. The designed controller is equally applicable if the desired dose is much smaller, such as $10 \text{ CEM43}^\circ T_{90}$, which is a typical goal during combination therapy.

A. Accurate Model, No Temperature Constraints

In this case, no parametric mismatch between the plant and its model is present. Fig. 6(a) and (b) is obtained with different values of the moving treatment horizon Δt , (15 and 35 s, respectively), and shows the temperature trajectories in several spatial locations: In the normal tissue before the tumor, $x = 2$; Inside the tumor close to the focal zone of the transducer, $x = 5.5$; In deep-seated normal tissue, $x = 10$. The T_{90} temperature inside the tumor is also shown. Fig. 6(c) and (d) shows the delivered thermal dose and the corresponding control power input for two different values of Δt . When $\Delta t = 15$ s, the controller operates at the power constraint, resulting in near time optimal treatment. The controller switches the power from the upper to the lower constraint at $t = 91$. The final thermal dose delivered during the treatment is approximately 300 cumulative equivalent minutes, which is substantially larger than the desired $240 \text{ CEM43}^\circ T_{90}$. The overdose is caused by a slightly longer than optimal time when the power is maintained at its upper constraint: The optimal switching time is between 90 and 91 s, and cannot be achieved with a 1 s sampling rate. Switching power off at 90 s will lead to undertreatment of the target. In general, a much faster update of the control input is required during high temperature therapies to avoid overdosing in the case when a substantial dose accrues during the tissue cooling process, as is the case with poorly perfused tumors.

The strong nonlinearity between highly elevated temperatures and the thermal dose is clearly evident in this example. Also note that a very large residual thermal dose is delivered during the cooling of the tissue. The value of the residual thermal dose strongly depends on the thermal properties of the tissue, of which blood perfusion is usually not only the most important, but is also very site- and patient-specific.

A less aggressive tuning of the TD controller with $\Delta t = 35$ leads to the precise delivery of the desired reference thermal dose. The control input remains near optimal. However, in this case the reference (linear) trajectory for the thermal dose is closely followed at the end of the treatment with the control input other than the extreme values of $u = u_{\max}$ and $u = 0$. Further increase of Δt will lead to an even longer treatment, and further deviation from the time optimal control policy.

Remark 1—In this paper, the treatment time t_{treat} is defined as the time during which the controller remains active (i.e., $u(t) \equiv 0$ for all $t > t_{\text{treat}}$). Fig. 6 indicates that during time-suboptimal treatment, the controller remains active for approximately 220 s compared to less than 100 s in the optimal case. However, the T_{90} temperature remains above 39°C for approximately the same period and, as a result, the final treatment dose is reached at approximately the same time in both cases.

Remark 2—The correlation between the time when D_f is reached and t_{treat} is weak only in low perfusion cases. For high-perfusion targets (e.g., prostate and brain tumors), which require long treatment time, the situation is different since the final dose is reached at approximately t_{treat} . Thus, for high perfusion targets, the time-optimal treatment is desirable. The minimum time control is even more important when the treatment is carried out using multiple focal zones obtained by electronically steering a phased-array or mechanically repositioning a single focused transducer. In this case, the dose continues to be delivered as tissue cools in the previously treated zone, while the power is applied in a new location.

B. Parametric Modeling Error, No Constraints

For the case of $\Delta t = 15$, simulations are performed to ascertain the robustness of the controller to plant-model mismatch. Fig. 7(a) depicts the results when the perfusion in the patient's tumor has changed from 5 to 3 kg/m³ s, while the predictive model, used by the controller, retains the original value. This scenario reflects the fact that the blood flow in the tumor can change in unpredictable and unknown ways. Despite a substantial patient-model mismatch, the controller is able to maintain a near time-optimal treatment schedule. The treatment time is approximately the same as with higher perfusion, but the controller maintains the input at its upper constraint for a shorter period of time. In the last 60 s of the treatment, the controller gradually reduces the power to zero, which prevents overdosing. A value of Δt shorter than 15 s leads to an instantaneous switching off of the power but results in overdose to the tumor.

C. Parametric Modeling Error, Constrained Temperature

This case is identical to the preceding case, except that the following constraint on the maximum temperature in the normal tissue is imposed: The temperature elevation $T(t)$ must not exceed 7°C at $x = 2$. As evident from Fig. 7(b), the constraint is met, but it is necessary to substantially prolong the treatment compared to the unconstrained case of Fig. 7(a) in order to reach the desired setpoint of 240 CEM43° T_{90} . Note that the controller essentially operates with either power or temperature constraints active, indicating that minimum-time treatment is attained. There is no error between the delivered thermal dose and D_f which is possible because of substantially lower temperatures reached in the tumor and the consequent lower residual thermal dose delivered during cooling. Controlling the treatment at active temperature constraint in the normal tissue leads to essentially constant T_{90} and linear trajectory of the thermal dose during much of the treatment. The treatment time with temperature constraints may be reduced with a highly focused moving or phased-array transducer, which enables a localized multi-zone treatment of the target.

V. Discussion and Conclusions

Traditionally, the problem of controlling thermal treatments is formulated as a temperature control problem. Because it is generally impossible to control the temperature distribution of the entire target (an underactuated problem of controlling an infinite-dimensional system with a limited number of manipulated variables), most previous work, e.g., [12] and [13], was concentrated on controlling temperature in several point-wise locations. The alternative approach of directly controlling the thermal dose is advocated in this paper. Our decision is primarily motivated by the following factors.

1. The thermal dose is a measure of clinical efficacy of thermal treatments, though the most appropriate form of the TD relationship is still under investigation.
2. Maintaining the desired time-invariant temperature distribution with the currently available noninvasive ultrasound or radio frequency actuators is an underactuated (and thus infeasible) control problem. At the same time, there is generally an infinite number of time varying distributions $T(t, y, z)$, such that the nonlinear temperature integrator (1) or (2) achieves the desired values. Thus, control of the thermal dose is a well-posed problem.
3. Since we have a choice of time-varying temperature distributions which leads to the desired TD, the problem of selecting the time optimal treatment can be posed. Furthermore, we can require that certain constraints are met, which may include the requirement of maintaining the normal tissue temperature in the selected spatial locations below the specified peak value. However, very stringent temperature

constraints may lead to an infeasible control problem, or require a very long treatment time.

The design of the thermal dose controller is a challenging problem owing to highly nonlinear temperature-dose relationship, system aftereffect, and actuator and normal tissue constraints. The first effort toward direct control of the thermal dose in thermal therapies [14], [15] required continuous linearization of the dose-temperature relationship. This restricted the applicability of the developed controller to the cases with relatively small temperature variability, and led to longer treatment times. The controller developed in this paper removes these limitations, making it applicable to a broad range of thermal therapies, including HIFU and other high-temperature therapies.

The proposed controller has a cascade structure. The main nonlinear thermal dose controller dynamically generates the updated reference temperature trajectory for the secondary temperature controller. The temperature controller is implemented as a linear, constrained MPC. The model predictive controller ensures that the maximum allowable temperature constraints in the normal tissue are not violated, and its predictive capability accounts for the residual thermal dose delivered when the transducer is switched off, which can be significant for low perfusion targets. The developed thermal dose controller is a computationally efficient, inversion-based, nonlinear controller that updates the reference trajectory for the MPC based on the difference between the desired and the delivered thermal dose. The simple and intuitive tuning of the thermal dose controller depends on a single parameter—the moving treatment horizon Δt . It is shown that by selecting the treatment horizon a near time-optimal progression of the thermal treatments can be enforced without explicit on-line solution of the minimum-time optimal control problem.

Using 1-D simulations, it is shown that the desired thermal dose is delivered to the tumor even in the presence of a significant plant-model mismatch, and without violating constraints on normal tissue temperature. Simulation results, Fig. 7(b), show that the controller operates with either normal tissue temperature and/or transducer saturation constraints active, which is necessary to minimize the treatment time. The experimental validation of the developed approach [17] shows an excellent agreement with the simulation results.

This paper details the theoretical development of the proposed approach to the control of thermal therapies and demonstrates its application to a 1-D case using computer simulations. The successful experimental testing of the developed controller with thin cylindrical phantoms [17] and *in vivo* canine muscle [18] was recently reported. The proposed approach is applicable to three-dimensional targets of clinical interest and can be modified for the case of moving and phased array transducers, which is the subject of ongoing research.

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References

1. Dewhirst MW, Sneed PK. Those in gene therapy should pay closer attention to lessons learnt from hyperthermia. *Int J Radiat Oncol: Biol, Phys.* 2003; 57:597–599. [PubMed: 12957278]
2. van der Zee J, Hulshof MCM. Lessons learned from hyperthermia. *Int J Radiat Oncol: Biol, Phys.* 2003; 57:596–597. [PubMed: 12957277]

3. Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach JK, Baum J, Singer S, Jolesz FA. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: A feasibility study. *Radiology*. 2001; 219:176–185. [PubMed: 11274554]
4. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Oncol Biol Phys*. 1984; 10:787–800.
5. Thrall DE, Rosner GL, Azuma C, Larue SM, Case BC, Samulski T, Dewhirst MW. Using units of CEM 43°C T_{90} , local hyperthermia thermal dose can be delivered as prescribed. *Int J Hypertherm*. 2000;415–428.
6. Leopold KA, Dewhirst MW, Samulski TV, Dodge RK, Georg SL, Blivin JL, Prosnitz LR, Oleson JR. Cumulative minutes with greater than temindex is predictive of response of superficial malignancies to hyperthermia and radiation. *Int J Radiat Oncol: Biol, Phys*. 1993; 25:841–847. [PubMed: 8478235]
7. Maguire PD, Samulski T, Prosnitz LR, Jones EL, Powers B, Layfields LW, Brizel DM, Scully SP, Harrelson JM, Dewhirst MW. A phase II trial testing the thermal dose parameter CEM43 as a predictor of response in soft tissue sarcomas treated with pre-operative thermoradiotherapy. *Int J Hypertherm*. 2001; 17:283–290.
8. Sherar M, Liu FF, Pintilie M, Levin W, Hunt J, Hill R, Hand J, Vernon C, van Rhoon G, van der Zee J, Gonzalez GD, van Dijk J, Whaley J, Mackin D. Relationship between thermal dose and outcome in thermoradiotherapy treatments for superficial recurrences of breast cancer: Data from phase III trial. *Int J Radiat Oncol: Biol, Phys*. 1997; 39:371–380. [PubMed: 9308941]
9. Skliar, M.; Arora, D.; Roemer, RB. Control of nonlinear integrators. presented at the AICHE Annu. Meeting; Indianapolis, IN. Nov. 2002;
10. Kolmogorov, AN.; Fomin, SV. Introductory Real Analysis. New York: Dover; 1975.
11. Kolmanovskii, V.; Myshkis, A. Introduction to the Theory and Application of Functional Differential Equations. Dordrecht, The Netherlands: Kluwer; 1999.
12. Hutchinson EB, Dahleh M, Hynynen K. The feasibility of MRI feedback control for inter-cavitary phased array treatments. *Int J Hypertherm*. 1998; 11:39–56.
13. Salomir R, Palussière J, Vimeux FC, de Zwart JA, Quesson B, Gauchet M, Lelong P, Pergrale J, Grenier N, Moonen CTW. Local hyperthermia with MR-guided focused ultrasound: Spiral trajectory of the focal point optimized for temperature uniformity in the target region. *J Mag Reson Imag*. 2000; 12:571–583.
14. Arora D, Skliar M, Roemer RB. Model-predictive control of hyperthermia treatments. *IEEE Trans Biomed Eng*. Jul; 2002 49(7):629–639. [PubMed: 12083297]
15. Arora, D.; Skliar, M.; Roemer, RB. Model predictive control of the ultrasound hyperthermia treatment of cancer. *Proc. 2002 Am. Control Conf.*; Anchorage, AK. May 2002; p. 2897-2902.
16. Damianou C, Hynynen K. Focal spacing and near-field heating during pulsed high temperature ultrasound therapy. *Ultrasound Med Biol*. 1993; 19:777–787. [PubMed: 8134978]
17. Arora, D.; Skliar, M.; Cooley, D.; Blankespoor, A.; Moellmer, J.; Roemer, RB. Nonlinear model predictive thermal dose control of thermal therapies: Experimental validation with 1-D phantoms. *Proc. 2004 Am. Control Conf.*; Boston, MA. 2004. p. 1627-1632.
18. Arora, D.; Cooley, D.; Perry, T.; Blankespoor, A.; Skliar, M.; Roemer, RB. *In vivo* evaluation of a model predictive thermal dose controller. presented at the 9th Int. Congr. Hyperthermic Oncology (ICHO'2004); St. Louis, MO. Apr. 2004;
19. Arora D, Cooley D, Perry T, Blankespoor A, Skliar M, Roemer RB. Thermal dose control of focused ultrasound treatments: Phantom and *in vivo* evaluation. *Phys Med Biol*. 2004 to be published.
20. Pennes HH. Analysis of tissue and arterial blood temperatures in resting human forearm. *J Appl Physiol*. 1948; 1:93–122. [PubMed: 18887578]
21. Roemer RB, Dutton AW. A generic tissue convective energy balance equation: Part I theory and derivation. *ASME J Biomech Eng*. 1998; 120:395–404.
22. Kolios MC, Worthington AE, Sherar MD, Hunt JW. Experimental evaluation of two simple thermal models using transient analysis. *Phys Med Biol*. 1998; 43:3325–3340. [PubMed: 9832019]
23. Wissler EH. Pennes' 1948 paper revisited. *J Appl Physiol*. 1998; 85:35–41. [PubMed: 9655751]

24. Sekins, KM.; Emery, A. Therapeutic heat and cold. In: Lehmann, J., editor. Thermal Science for Physical Medicine. Baltimore, MD: Williams and Wilkins; 1982. p. 70-132.
25. Sekins KM, Lehmann JF, Esselmann P, Dundore D, Emery AF, Delateur BJ, Nelp WB. Local muscle blood flow and temperature responses to 915 MHz diathermy as simultaneously measured and numerically predicted. Arch Phys Med Rehab. 1984; 65:1-7.
26. Moros EG, Dutton A, Roemer R, Burton M, Hynynen K. Experimental evaluation of two simple thermal models using hyperthermia in muscle *in vivo*. Int J Hypertherm. 1993; 9:581-598.
27. Strobehn J, Curtis EH, Paulsen KD, Yuan X, Lynch DR. Optimization of the absorbed power distribution for an annular phased array hyperthermia system. Int J Radiat Oncol, Biol, Phys. 1989; 16:589-599. [PubMed: 2921161]
28. Knudsen M, Overgaard J. Identification of thermal model in human tissue. Int J Hypertherm. 1986; 2:21-38.
29. Christensen, DA. Ultrasonic Bioinstrumentation. New York: Wiley; 1988.
30. Hynynen, K. Methods of external hyperthermic heating. In: Gautherie, M., editor. Biophys Tech Ultrasound Hypertherm. Springer; 1990. p. 61-115.
31. Akyurekli D, Gerig LH, Raaphorst GP. Changes in muscle blood flow distribution during hyperthermia. Int J Hypertherm. 1997; 13:481-196.
32. Malinen M, Huttunen T, Kaipio J. An optimal control approach for ultrasound induced heating. Int J Control. 2003; 76:1323-1336.
33. Roemer RB. Engineering aspects of hyperthermia. Ann Rev Biomed Eng. 1999; 1:347-376. [PubMed: 11701493]
34. Eisen, M. Mathematical Models in Cell Biology and Cancer Chemotherapy. New York: Springer-Verlag; 1979.
35. Pontryagin, LS.; Boltyanskii, VG.; Gamkrelidze, RV.; Mishchenko, EF. The Mathematical Theory of Optimal Processes. New York: Wiley; 1962.
36. Hazle JD, Stafford RJ, Price RE. Magnetic resonance imaging-guided focused ultrasound thermal therapy in experimental animal models: Correlation of ablation volumes with pathology in rabbit muscle and VX2 tumors. J Magn Reson Imag. 2002; 15:185-194.
37. Kangasniemi M, Diederich CJ, Price RE, Stafford RJ, Schomer DF, Olsson LE, Tyreus PD, Nau WH, Hazle JD. Multiplanar MR temperature-sensitive imaging of cerebral thermal treatment using interstitial ultrasound applicators in a canine model. J Magn Reson Imag. 2002; 16:522-531.

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Fig. 1.
One-dimensional inhomogeneous tissue model.

Fig. 2.
Power deposition as a function of depth inside the tissue.

Fig. 3.
Feedforward control of the thermal dose.

Fig. 4. Feedforward implementation of K_D with different parameterizations. First row: explicit parameterization $T_{90,\text{ref}}(t) = \text{const}$; identical to implicit parameterization P_{I1} . Second row: P_{I2} parameterization. Third row: P_{I3} parameterization. Solid lines indicate the reference trajectories for temperature and thermal dose. Dashed lines show the achievable trajectories with unconstrained MPC temperature controller.

Fig. 5.
Feedback control of the thermal dose.

Fig. 6. Case of accurate predictive model with no temperature constraints. (a) Temperature trajectories with $\Delta t = 15$ s. (b) Temperature trajectories with $\Delta t = 35$ s. (c) Thermal dose history. (d) Control input.

Fig. 7.

Case of plant-model mismatch: (A) Unconstrained case is shown in left column; (B) Constraint $T(t) - 7^{\circ}\text{C}$ at $x = 2$ is imposed. In both cases, $\Delta t = 15$.

Table I

Tissue Properties of Human Tissue, [28] and [29]

	k W/(m °C)	ρ kg/m ³	$C = C_b$ J/(kg °C)	α N/m
Muscle	0.64	1000	3500	18.5
Tumor	0.57	1000	4000	20.5