Effective learning strategies for real-time image-guided adaptive control of multiple-source hyperthermia applicators

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Purpose: This paper investigates overall theoretical requirements for reducing the times required for the iterative learning of a real-time image-guided adaptive control routine for multiple-source heat applicators, as used in hyperthermia and thermal ablative therapy for cancer.

Methods: Methods for partial reconstruction of the physical system with and without model reduction to find solutions within a clinically practical timeframe were analyzed. A mathematical analysis based on the Fredholm alternative theorem (FAT) was used to compactly analyze the existence and uniqueness of the optimal heating vector under two fundamental situations: (1) noiseless partial reconstruction and (2) noisy partial reconstruction. These results were coupled with a method for further acceleration of the solution using virtual source (VS) model reduction. The matrix approximation theorem (MAT) was used to choose the optimal vectors spanning the reduced-order subspace to reduce the time for system reconstruction and to determine the associated approximation error. Numerical simulations of the adaptive control of hyperthermia using VS were also performed to test the predictions derived from the theoretical analysis. A thigh sarcoma patient model surrounded by a ten-antenna phased-array applicator was retained for this purpose. The impacts of the convective cooling from blood flow and the presence of sudden increase of perfusion in muscle and tumor were also simulated.

Results: By FAT, partial system reconstruction directly conducted in the full space of the physical variables such as phases and magnitudes of the heat sources cannot guarantee reconstructing the optimal system to determine the global optimal setting of the heat sources. A remedy for this limitation is to conduct the partial reconstruction within a reduced-order subspace spanned by the first few maximum eigenvectors of the true system matrix. By MAT, this VS subspace is the optimal one when the goal is to maximize the average tumor temperature. When more than 6 sources present, the steps required for a nonlinear learning scheme is theoretically fewer than that of a linear one, however, finite number of iterative corrections is necessary for a single learning step of a nonlinear algorithm. Thus, the actual computational workload for a nonlinear algorithm is not necessarily less than that required by a linear algorithm.

Conclusions: Based on the analysis presented herein, obtaining a unique global optimal heating vector for a multiple-source applicator within the constraints of real-time clinical hyperthermia treatments and thermal ablative therapies appears attainable using partial reconstruction with minimum norm least-squares method with supplemental equations. One way to supplement equations is the inclusion of a method of model reduction. © 2010 American Association of Physicists in Medicine. [DOI: 10.1118/1.3302829]

Key words: feedback control, adaptive control, Fredholm alternative theorem, matrix approximation theorem, minimum norm least-squares solution, partial reconstruction

I. INTRODUCTION

In minimum time, delivering simultaneously therapeutic thermal dose in tumor and minimum dose in normal tissues is the essential and challenging goal of hyperthermia cancer treatment. Research in this field becomes increasingly important as a growing body of evidence demonstrates the effectiveness of local-regional hyperthermia using externally applied nonionizing heat sources together with radiation and chemotherapy.¹⁻³ However, the appealing features of hyperthermia are often limited by the lack of a robust controller capable of delivering a precise therapeutic thermal dose to the target using real-time feedback from high resolution three

dimensional temperature images such as magnetic resonance temperature images (MRTIs).⁴ Similar research trends were also reported for thermal ablation therapy by removing heat (cryoablation)¹ or by using nonionizing heat sources such as light amplification by simulated emission of radiation (laser), radio-frequency (RF), microwave (MW), and focused ultrasound (U.S.).^{1,5}

MRTI is an appealing noninvasive imaging technique during hyperthermia.^{6,7} Patients treated by hyperthermia or thermal ablative therapy and simultaneously under MRTI monitoring are relieved from suffering the risk of hemorrhage and infection caused by the use of traditional invasive temperature probes.⁸ For U.S. hyperthermia, MRTI has another

added benefit of eliminating interference of the inserted thermal probe on the measured temperature at the wavelength typically used for U.S. hyperthermia.⁹ Furthermore, use of MRTI is more attractive than using U.S. imaging because MRTI is sensitive to temperature and thus is capable of providing in real-time magnitude and extent of temperature elevations due to heating, which, in turn, allows on-line monitoring of the treatment effects.¹⁰ There are already literatures addressing the use of temperature monitoring using MRI during hyperthermia or thermal ablative therapy using different nonionizing heat sources such as RF,¹¹ U.S.,^{10,12} and laser.^{13,14}

MRI-guided feedback control of hyperthermia reportedly improves the treatment quality.^{15–17} For instance, Hutchinson *et al.* proposed a multi-input and multioutput (MIMO) linear quadratic regulator (LQR) controller using MRTI as feedback for U.S. prostate hyperthermia.¹⁵ This LQR controller was numerically validated being able to realize two-dimensional power focusing. Behnia *et al.* used a closed-loop feedback control of phased-array MW hyperthermia using MRTI feedback.¹⁶ Recently, Mougenot *et al.* suggested using a proportional, integral, and derivative (PID) automatic temperature control for U.S. hyperthermia.¹⁷ This PID controller determines the optimal power deposition along a pre-specified three-dimensional heating trajectory. Its performance was investigated in experiments using phantom. Although these aforementioned feedback control methodologies demonstrated its ability to improve the quality of hyperthermia, its performance relies on closely the availability of accurate descriptions on the wave propagation and the bio-heat transfer process models and the associated parameter values.¹⁸ Nevertheless, a theoretically rigorous and experimentally validated bioheat transfer model is not available.¹⁹ Besides, the electric properties such as electric permittivity and conductivity, the thermal properties such as thermal conductivity, and blood perfusion are patient specific and can be deviated from the tabulated values.^{20–22} These inaccuracies degrade the reliability of the mathematical model and thus the performance of feedback controller. Hence, a research direction is to investigate the potential of MRI-guided adaptive control of hyperthermia^{23–28} or thermal ablative therapy.^{1,14}

The essential structure of adaptive control consists of an adaptive learning algorithm and a (traditional) feedback controller such as those mentioned in the previous paragraph. For example, Fuentes *et al.* used a least-squares error (LSE) based nonlinear learning algorithm to identify the parameters involved in laser cancer treatment.¹⁴ Once these patient-specific parameters were identified, an optimal control of laser heat source was applied.¹⁴ In order to maintain the most currently updated patient-specific parameters during a treatment, Kowalski and Jin combined an LSE learning algorithm with a PI feedback controller for electromagnetic (EM) hyperthermia.²³ *In situ* system information was identified before therapeutic heating and then kept on updating throughout the treatment using a recursive LSE learning algorithm, and the PI controller determined the driving vector exciting

the antenna applicator to meet the goal of selective tumor heating.²³

The challenges for designing an effective adaptive controller are rooted in the competing requirements of accurate focusing and the timely delivery of the applied power deposition. Using more heat sources enhances the spatial focus of heating, at the expense of significantly increased time expenditure for system reconstruction.^{23–25} A traditional approach is to perform full reconstruction of the system for determining the optimal heating vector.^{23,14} The full reconstruction can require hours for a modern phased-array applicator formed from many independent heat sources for more accurate spatial power focusing.^{24,25} In contrast, a more recent approach is to determine the optimal heating vector after a timely partial reconstruction that resolves its intrinsic mathematical challenge of uniquely determining a reliable optimal heating vector using fewer than required equations. This attractive and trendy approach of partial reconstruction was investigated using both linear²⁴ and nonlinear²⁵ algorithms. Recent investigations have incorporated a method of model reduction using virtual source²⁹ (VS) to accomplish even shorter solution times for system reconstruction that are compatible with clinical treatment timeframe (e.g., 60 min).^{26,27}

This paper lays the theoretical foundation for designing one such robust real-time image-guided adaptive control of local-regional hyperthermia and other thermal ablative modalities to address all the aforementioned challenges. First demonstrated is that theoretically, partial reconstruction using linear reconstruction cannot guarantee sufficient speed of the reconstruction process. Since the essential structure of a nonlinear reconstruction is linearization followed by iterative search based on the linearized system, partial reconstruction using nonlinear reconstruction also suffers this theoretical limitation. Simple numerical examples are presented to illustrate this theoretical consequence. By the analysis that will be provided herein, partial reconstruction incorporating with a method of model reduction is the key to accelerate the reconstruction process. Numerical demonstrations of this result will be given for a model of human leg with soft tissue sarcoma tumor placed inside a ten-antenna annular phased-array applicator. Two operating frequencies were simulated, 138 and 150 MHz, for different models (see details in Sec. II). Convective cooling from blood flow was included in the simulations. In addition, blood perfusion that has a sudden increase in time was also simulated.

II. ESSENTIAL THEORETICAL BASES OF CONTROLLER

Blood flow has been shown to significantly affect the therapeutic outcomes of hyperthermia and thermal ablative therapy.^{30–33} The influences of blood flow on hyperthermia and thermal ablative therapy are mainly attributable to the convective cooling from flow motion and heat sink from blood perfusion. A practical approximate model simulating these effects is given below in tensor form [Eq. (1), Pennes bioheat equation],

$$\rho \cdot C_i \cdot \left(\frac{\partial T}{\partial t} + v_i \cdot \frac{\partial T}{\partial x_i} \right) = \frac{\partial}{\partial x_i} \left(k \cdot \frac{\partial T}{\partial x_i} \right) - w_b \cdot C_b \cdot (T - T_b) + Q, \quad i = x, y, z. \quad (1)$$

Here ρ is density, C_i denotes specific heat, v_i represents the flow velocity inside blood vessels, k is thermal conductivity, w_b means Penne blood perfusion,³⁴ C_b is the specific heat of blood, T_b denotes the temperature of blood, and Q is the power source. All of these parameters can be functions of temporal and spatial variables for the derivation of the temperature solution of this equation. However, in practice, only the velocity of blood, the Pennes perfusion, and the power source are functions of time and space. Other parameters are only functions of space. The Pennes perfusion can be a function of temperature,^{35–38} but this case is not addressed here. Interested readers are referred to other recent studies.^{26,27,39} The above Pennes bioheat transfer equation³⁴ (BHTE) describes the energy balance between power input from an ex-

ternal hyperthermic applicator and heat losses in living tissue from convective (blood flow) and conductive heat transfer.³⁴ The cooling term to approximate cooling by perfusion was introduced because the simulation of blood flow in a complex vessel network is computationally too expensive. The use of this term was validated experimentally as a practical approximation for blood cooling in the absence of thermally significant vessels.

Assuming linear wave propagation and thermal dissipation, a recent study²⁴ presented a formulation using Green's function of the bioheat transfer equation. The formulation was given by assuming that tissue temperatures are elevated by a set of EM wave sources. The formulation becomes simpler when U.S. wave sources are employed. The formulation directly relates the temperatures inside a patient with the control variables: The phase and magnitude of each independent antenna, as shown in Eqs. (2),

$$\begin{aligned} T(t, \vec{r}) &= \int_{\tau=0}^t \int_{V'} (G(t - \tau, \vec{r} - \vec{r}') \cdot P_{\text{sum}}(\tau, \vec{r}')) \cdot dV' \cdot d\tau \\ &= \vec{u}^H \cdot \left(\frac{\sigma}{2} \cdot \int_{\tau=0}^t \int_{V'} (G(t - \tau, \vec{r} - \vec{r}') \cdot (E_{M \times 3}^H \cdot E_{3 \times M}(\tau, \vec{r}'))) \cdot dV' \cdot d\tau \right) \cdot \vec{u} \\ &= \vec{u}_{1 \times M}^H \cdot S_{M \times M}(t, \vec{r}) \cdot \vec{u}_{M \times 1}, \end{aligned} \quad (2a)$$

$$P_{\text{sum}} = \frac{\sigma}{2} \cdot \vec{E}_{\text{sum}}^H \cdot \vec{E}_{\text{sum}} = \frac{\sigma}{2} \cdot \vec{u}^H \cdot E_{M \times 3}^H \cdot E_{3 \times M} \cdot \vec{u}, \quad (2b)$$

$$\vec{E}_{\text{sum}} = \sum_{m=1}^M \vec{E}_m \cdot u_m = E_{3 \times M} \cdot \vec{u}. \quad (2c)$$

In Eqs. (2), the vector r is a function of the x , y , and z variables denoting the position in space, and the indices i , j , and k are node indices along the x , y , and z directions. The variable σ denotes the electric conductivity and the superscript H denotes complex conjugate transpose. The variable M is the number of independent antennas, the vector E_m is the electric field (E -field) from antenna m , and u_m is the m th (complex) antenna setting. The term P_{sum} represents the power deposition produced from all heat sources. The matrix S is a transfer function at each point.

Adaptive control is retained to accomplish the power focusing and to regulate the temperature elevation. The control is divided into three stages; essential system information is retrieved for iterative reconstruction of the system, the optimal driving vector for the applicator to deposit power concentrated in the tumor is determined according to the imposed optimal criterion, and then a power regulator is applied. A generalized form of the central formula for the design of linear adaptive control using Eq. (2) based on different optimization criteria^{40,41,24} is shown in Eqs. (3),

$$T_{\text{representative}}(t) = \vec{u}^H \cdot S_{\text{representative}}(t) \cdot \vec{u}, \quad (3a)$$

$$S_{\text{representative}} = \frac{1}{N_{\text{total tumor points}}} \cdot \sum_{n \in \text{tumor region}} a_n \cdot S_n(t, \vec{r}_n), \quad (3b)$$

or,

$$S_{\text{representative}} = \frac{\frac{1}{N_{\text{total tumor points}}} \cdot \sum_{n \in \text{tumor region}} a_n \cdot S_n(t, \vec{r}_n)}{\frac{1}{N_{\text{total normal tissue points}}} \cdot \sum_{n \in \text{normal tissue regions}} b_n \cdot S_n(t, \vec{r}_n)}. \quad (3b')$$

Once this representative system matrix ($S_{\text{representative}}$) having a number of M^2 unknown variables is fully reconstructed,^{24,39} its eigenvector corresponding to its maximum eigenvalue is the optimal heating vector fulfilling the imposed optimal goal, e.g., simultaneously satisfying the therapeutic and safety needs of hyperthermia. Challenges arise when one aims to determine the optimal heating vector with the least amount of clinical times to identify this representative system. One must also consider the effects of unavoidable errors and or uncertainties associated with feedback measurements such as MRT images.²⁴

The other approach formulates the problem of system reconstruction in nonlinear form below,

$$T(t, \vec{r}) = \vec{u}^H \cdot \left(\frac{\sigma}{2} \cdot \int_{\tau=0}^t \int_{V'} (G(t - \tau, \vec{r} - \vec{r}') \times (E_{M \times 3}^H \cdot E_{3 \times M}(\tau, \vec{r}')) \cdot dV' \cdot d\tau \right) \cdot \vec{u}. \quad (4)$$

Here the aim is to reconstruct the (unknown) system described by the E -matrix. This formulation is second order since it involves a multiplication of the E -matrix. This formulation involves 6^*M (real) unknowns to be inversely identified.^{25,39}

In the past, a full reconstruction of this representative matrix was employed.^{40,42,23} Full reconstruction approach can require intolerably long solution times to retrieve the essential patient-applicator information, e.g., several hours if a multiring, multi-antenna applicator such as the 12 antenna 100 MHz BSD-2000 Sigma-Eye applicator (BSD Corporation, Salt Lake City, UT) is employed.^{24,25} A practical work around was to use a partial reconstruction scheme that allows determining the optimal heating vector without the more time-consuming full reconstruction of the system. But this approach requires more careful analysis to ensure the existence and uniqueness of its solution. Since the system reconstruction described by Eqs. (3) is a linear problem whether full or partial, a mathematical analysis based on the Fredholm alternative theorem⁴³ (FAT) is conducted. The nonlinear formulation represented by Eq. (4) is also analyzed using FAT,⁴³ since the generic way to solve a nonlinear problem consists of linearization followed by iterative correction.

The Fredholm alternative theorem states: "Given a linear system of equations, its solution exists only when its right hand side totally falling within the range of this linear map. The solution, if exists, is unique only if the null space of this

linear map is trivial, i.e., consisting only zero component." The FAT can be described using the following two explicit mathematical expressions:

$$A_{M \times N} \cdot \vec{x}_{N \times 1} = \vec{b}_{M \times 1} \text{ has a solution}$$

$$\Leftrightarrow \vec{b}_{M \times 1} \in \text{Range}(A_{M \times N})$$

$$\Leftrightarrow \langle \vec{b}_{M \times 1}, \vec{v}_{M \times 1} \rangle = 0, \quad \forall \vec{v}_{M \times 1} \in \text{Null}(A_{N \times M}^A), \quad (5a)$$

$$\text{The solution to } A_{M \times N} \cdot \vec{x}_{N \times 1}$$

$$= \vec{b}_{M \times 1} \text{ is unique} \Leftrightarrow \text{Null}(A_{M \times N}) = 0. \quad (5b)$$

The superscript A denotes adjoint; it is transpose when the matrix is real, complex conjugate transpose when complex. This paper uses FAT to analyze the mathematical conditions required for the existence and uniqueness of the solution to a real-time MRTI-guided control of hyperthermia treatment.

Next, another theorem, the matrix approximation theorem (MAT),^{44,45} is introduced for investigating the best reduced-order approach to realize accurate spatial focal heating within the tumor in a minimum amount of time expenditure. The MAT states: "Given a matrix, A , with rank k , its best approximate matrix having rank r ($< k$) is given by the partial sum of first r outer product of its left and right singular vectors, each having a weight of the associated first maximum singular value. The estimate of the error in the Frobenius norm from this approximation is the square root of the sum of squares of the singular values corresponding to the neglected terms. If the metric of the error is in the matrix 2-norm, then it is the $(r+1)^{\text{th}}$ singular value."

The explicit mathematical description of MAT is also given here. Let A be an M -by- N matrix of rank k and write its singular value decomposition below,

$$A = \sum_{i=1}^k \sigma_i \cdot \vec{u}_i \cdot \vec{v}_i^A, \quad \sigma_i > 0. \quad (6a)$$

Given a number $r < k$, its best rank- r approximation is expressed below,

$$\tilde{A}_r = \sum_{i=1}^r \sigma_i \cdot \vec{u}_i \cdot \vec{v}_i^A. \quad (6b)$$

The associated approximation error is written as follows:

$$\begin{aligned} \text{Estimate in matrix 2-norm: } \min_{\text{rank}(\tilde{A})=r} \|A - \tilde{A}\|_2 &= \|A - \tilde{A}_r\|_2 \\ &= \sigma_{r+1} \end{aligned} \quad (6c)$$

or

$$\begin{aligned} \text{Estimate in the Frobenius norm: } \min_{\text{rank}(\tilde{A})=r} \|A - \tilde{A}\|_F &= \|A - \tilde{A}_r\|_F \\ &= \sqrt{\sum_{i=r+1}^k \sigma_i^2} \end{aligned} \quad (6c')$$

III. CONTROLLER INVOLVING THE MODEL REDUCTION OF VS

To further reduce the problem complexity, the model reduction of VS (Ref. 29) was employed for the numerical simulations. The model reduction of VS (Ref. 29) suggests projecting the physical variables (magnitude and phase of each antenna of the applicator) onto a smaller subspace spanned by a set of orthonormal VS basis vectors. Those orthonormal VS basis vectors are determined as the first N eigenvectors corresponding to the first N largest eigenvalues of the original representative system matrix that maximizes the algebraically average tumor temperature.²⁹ The mathematical expression of this approach is given below,

$$\begin{aligned} T_{\text{representative}}(t) &\approx (V_{M^2 \times N} \cdot \vec{u}_{N \times 1, \text{VS}})^H \cdot S_{M^2 \times M^2, \text{representative}} \\ &\quad \cdot (V_{M^2 \times N} \cdot \vec{u}_{N \times 1, \text{VS}}), \quad N < M^2. \end{aligned} \quad (7)$$

The reduced-order adaptive controller was designed to iteratively reconstruct the system confined in a smaller VS subspace spanned by the first N eigenvectors of the representative system matrix of the (original) Pennes BHTE with modification to include thermal effects from blood vessel [Eq. (1)]. The iterative reconstruction was started after applying the N VS basis vectors one at a time to heat the patient. Each update session consists of a heat-up and cool-down period. The times for these periods remained constant throughout the entire hyperthermia treatment. The difference between the temperature at the end of the heat-up period and the one at the end of the cool-down period of the previous update session was taken for the purpose of system reconstruction. Starting from the $(N+1)$ th step, the driving vector was determined as the maximum eigenvector of the representative system matrix just reconstructed using the N MRTI feedbacks. Thereafter, the representative system matrix was updated in minimum norm least-squares errors (MNLSE) sense after a new driving vector was used.

IV. NUMERICAL CONFIGURATIONS

Theoretical analyses are presented in Sec. V for cases analyzed under “basic” or “practical” treatment conditions. Numerical exhibitions will also be given. A simpler model is useful for understanding the basic analysis, and a more detailed model is required for realistic settings for the practical analysis.

IV.A. Simple Model

A simple approximate physical model is given below for numerical exhibition for a single step of system reconstruction,

$$\begin{aligned} \rho \cdot C_t \cdot \frac{dT}{dt} &= -w_b \cdot C_b \cdot T + \frac{\sigma}{2} \cdot \vec{E}_{\text{sum}}^H \cdot \vec{E}_{\text{sum}}, \\ \vec{E}_{\text{sum}} &= \sum_{m=1}^M \vec{E}_m \cdot u_m. \end{aligned} \quad (8)$$

Here M is the number of heating antennas, the vector E_m is the electric field from antenna m , u_m is the m th (complex) antenna setting, ρ denotes tissue density, C_t denotes the specific heat, w_b is the blood perfusion, and C_b refers to the specific heat of blood. By including the blood perfusion term, a known essential factor affecting hyperthermic outcomes, this model is more realistic than what was used by the Hyperthermia Group in Berlin,²⁵ from which they derived their adaptive control of image-guided hyperthermia using a nonlinear learning approach.

There are two independent point-heat sources in this model. The electric and thermal property values^{20-22,46} involved for the numerical demonstrations are given as those for (human) muscle when the working frequency of the EM wave is 150 MHz. The electric permittivity is 5.507×10^{-10} F/m, the electrical conductivity is 0.727 S/m, the permeability is $4 \cdot \pi \cdot 10^{-7}$ H/m, the density is 1050 kg/m³, the specific heat of muscle is 3639 J/kg/K, the specific heat for blood is 3770 J/kg/K, and the blood perfusion is 3.6 kg/m³/s. Initial temperature is assumed zero and the heating duration is 120 s, a value derived from previous clinical experience.⁴²

Commercial software MATLABTM (The MathWorks, Inc., Natick, MA) is used to conduct numerical experiments on numerical matrix inversion and the determination of the null space of a given matrix.

IV.B. Practical Model

A realistic model was built from a set of computerized tomography (CT) x-ray images for a patient with thigh sarcoma treated in a ten-antenna phased-array applicator²⁹ (Fig. 1). The MR-compatible applicator is enclosed by an MR bore (see Fig. 1). Tissue property values were obtained from the literature.^{20-22,31,47,48,46} The values are listed in Table I.

Finite element (FE) software (HFSS-Ansoft Corporation, Pittsburgh, PA) was used to compute the electric field distribution in the patient and output the fields in a uniform spatial grid of 4 mm, (2) the electric fields are used as inputs to an in-house developed finite difference software to compute the thermal distribution. A constant uniform water bolus temperature of 37 °C is used as the boundary condition.

The electric field distribution of the patient model was iteratively reconstructed. Each partial reconstruction session consists of a 1 min heat-up followed a 2 min cool-down. Gaussian noise having a standard deviation of 1.0 °C is

FIG. 1. Sketch showing the two legs of the patient and the heating facilities: A ten-antenna phased-array applicator enclosed by a MR bore. The cylindrical applicator is positioned uniformly around a cylindrical surface (human leg with tumor). The angle between two adjacent antennas is 36° . The diameter and length of the cylinder are 23 and 24 cm, respectively.

added to the numerically simulated MRTI feedback response as a stringent test of the unavoidable noise associated with any MRTI in practice.

Numerical simulations were performed using the practical patient model [Eq. (1)] having a sarcoma in the right thigh (Fig. 1). The tumor extended from -4.8 to 0.8 cm in x direction, from -14 to -9.6 cm in y direction, and from -7.6 to 5.6 cm in z direction. Two types of reduced-order VS subspace were investigated: (1) VS subspace built from the average tumor matrix and (2) VS subspace built from the product of the inverse of the average normal tissue matrix and the average tumor matrix. These simulations will allow readers to compare the treatment outcomes when different reduced-order VS subspaces are retained to limit the iterative search space.

Lastly, the case when the blood perfusion varies temporally was also simulated. The perfusion values of muscle and tumor were increased from 3.6 to 7.2 $\text{kg}/\text{m}^3/\text{s}$ and from 1.8 to 2.7 $\text{kg}/\text{m}^3/\text{s}$, respectively, after 24 min the heating initiated. While all the tumor perfusions were increased, only the perfusions within a specified region of muscle were in-

creased. This region is from -4.8 to 4.8 cm in x direction, from -9.0 to -6.2 cm in y direction, and from -8.0 to -4.0 cm in z direction. Under this time-varying perfusion condition, the VS subspace was built from the first two, three, and four orthonormal eigenvectors of the average tumor matrix.

V. RESULTS AND DISCUSSION

V.A. Basic analysis

All real world measurements come with unavoidable noise. Therefore, FAT was used to compactly analyze the existence and uniqueness of the optimal heating vector for system reconstructions in the absence and presence of noise:

V.A.1. Noiseless partial reconstruction (NLPR)

To ensure the existence and uniqueness of the solution to full reconstruction of system, FAT demands that there must be at least M^2 different (image) feedbacks excited from the same number of excitations of M independent wave sources. The partial reconstruction will shorten the clinical times required because it uses less than M^2 excitations of the independent heat sources; however, this gives more unknowns than equations. As a result, infinitely many feasible solution candidates become available, according to FAT. For example, the reconstruction problem for Eq. (3) can be reformulated as solving a linear system of equations,

$$(1) \quad A = \begin{bmatrix} 1 & 2 & 3 \\ 5 & 3 & 4 \\ 2 & 1 & 2 \end{bmatrix},$$

$$\vec{b} = \begin{bmatrix} 1 \\ 2 \\ 3 \end{bmatrix} \Rightarrow \vec{x}_{\text{true}} = A^{-1} \cdot \vec{b} = \begin{bmatrix} 0.6000 \\ -4.6000 \\ 3.2000 \end{bmatrix},$$

$$(2) \quad A = \begin{bmatrix} 1 & 2 & 3 \\ 5 & 3 & 4 \end{bmatrix},$$

TABLE I. Tissue property values (assumed for 138 MHz, permittivity of vacuum, $\epsilon_0 = 8.854 \times 10^{-12}$ F/m and permeability of vacuum, $\mu = 4\pi \times 10^{-7}$ Henry/m. The permeabilities of all tissues were assumed to be equal to that of vacuum and the velocity of the blood flow is 5.0 cm/s.)

Matrix	Relative electric permittivity		Electrical conductivity σ (S/m)	Density ρ (kg/m^3)	Specific heat Ct (J/kg/K)	Thermal conductivity k (W/m/°C)	Blood perfusion w_b ($\text{kg}/\text{m}^3/\text{s}$)
	$\epsilon_R = \frac{\epsilon}{\epsilon_0}$						
Blood vessel	55.0		0.484	1050	3770	0.40	...
Blood	...		...	...	3770	...	...
Bone, cortical	14.6		0.068	1600	1420	0.65	0.0
Bone, marrow	6.17		0.024	1600	1420	0.65	0.117
Fat	5.88		0.037	880	2387	0.22	1.1
muscle	62.8		0.723	1050	3639	0.56	3.6
Tumor	68.0		0.895	1050	3639	0.56	1.8
De-ionized water	81.0		0.0002	996	4178	0.61	...

$$\vec{b} = \begin{Bmatrix} 1 \\ 2 \end{Bmatrix} \Rightarrow \vec{x}_{\text{MNLS}} = A^A \cdot (A \cdot A^A)^{-1} \cdot \vec{b} = \begin{Bmatrix} 0.1696 \\ 0.1345 \\ 0.1871 \end{Bmatrix}.$$

The superscript A denotes adjoint; it is transpose when the matrix is real, complex conjugate transpose when complex.

Sufficient equations are provided in case (1), and thus, according to FAT, one can obtain the true (unique) solution. In contrast, the number of equations is insufficient in case (2). Therefore, according to FAT, there are an infinite number of solutions, as expressed below.

$$A_{N \times M^2} \cdot (\vec{x}_{M^2 \times 1, \text{MNLS}} + c \cdot \vec{v}_{M^2 \times 1, \text{null}(A)}) - \vec{b}_{N \times 1} = \vec{0}_{N \times 1}, \quad c \text{ is any scalar number, and } N < M^2. \quad (9a)$$

The equation above exhibits the fact that adding a component from the null space of the matrix A in case (2) can still be a solution, since by definition, a null vector results in zero output from the matrix A . Moreover, the magnitude of this extra component can be arbitrarily large as illustrated in equation below. The null space in this case is of one dimension, and the null vector is given below,

$$A_{N \times M^2} \cdot (\vec{x}_{M^2 \times 1, \text{MNLS}} + 10^4 \cdot \vec{v}_{M^2 \times 1, \text{null}(A)}) - \vec{b}_{N \times 1} = \begin{bmatrix} 1 & 2 & 3 \\ 5 & 3 & 4 \end{bmatrix} \cdot \left(\begin{Bmatrix} 0.1696 \\ 0.1345 \\ 0.1871 \end{Bmatrix} + 10^4 \cdot \begin{Bmatrix} 0.0765 \\ -0.8412 \\ 0.5353 \end{Bmatrix} \right) - \begin{Bmatrix} 1 \\ 2 \end{Bmatrix} = 10^{-10} \cdot \begin{Bmatrix} -0.2910 \\ 0.5821 \end{Bmatrix}. \quad (9a')$$

Readers can see that adding an extra member of a magnitude of 10^4 from the null space of the matrix A to the minimum norm least-squares (MNLS) solution for case (2) still satisfies the original partial equation.

The clinical impact of this mathematical consequence is that an arbitrarily chosen solution among such infinitely many candidates will not guarantee treatment quality and the preciseness of spatial power focusing, since the determined solution could include arbitrarily large components [e.g., an error of an magnitude of 10^4 , as shown in Eq. (9a')] from the null space of this underdetermined linear map. This problem can be solved by using FAT to determine the unique MNLS solution, which totally eliminates any (redundant) components from the null space of this mapping.

To further convince readers, other numerical exhibitions are given using the simple model described by Eq. (8).

The closed form solution for T of the model is given below,

$$T(t) = \begin{bmatrix} u_1^c & u_2^c \end{bmatrix} \cdot \begin{bmatrix} 0.4657 & 0.8845 - 0.1934 \cdot i \\ 0.8845 + 0.1934 \cdot i & 2.7199 \end{bmatrix} \cdot \begin{Bmatrix} u_1 \\ u_2 \end{Bmatrix}. \quad (9a'')$$

Based on FAT, the full reconstruction of the matrix S requires

TABLE II. Excitation settings.

	First set	Second set	Third set	Fourth set
u_1	1	0	1	i
u_2	0	1	i	-i

four different excitations. Listed below is a set of four different excitations (Table II).

The outputs for T corresponding to the above excitations are (0.4657, 2.7199, 3.5724, 1.4167). Therefore, readers can form a system of linear equations to reconstruct the matrix S .

A partial reconstruction is considered using only the first two excitations and its corresponding outputs. This time the system is reconstructed in the sense of MNLS. The reconstructed S -matrix and its eigenpair are given as

$$S_{\text{MNLS}} = \begin{bmatrix} 0.4657 & 0 \\ 0 & 2.7199 \end{bmatrix},$$

$$\text{norm}(S_{\text{MNLS}}) = 2.7595,$$

$$V_{\text{MNLS}} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix},$$

$$D_{\text{MNLS}} = \begin{bmatrix} 2.7199 & 0 \\ 0 & 0.4657 \end{bmatrix}. \quad (9a''')$$

From this example above, readers can see that the MNLS solution to the true system matrix (S) is not the true (globally optimal) solution to the original problem. However, it serves as the optimal local solution to the original problem when only partial information is available.

Next, a numerical example is given to illustrate the consequence of using the first and third measurements to reconstruct the system in the sense of MNLS,

$$S_{\text{MNLS}} = \begin{bmatrix} 0.4657 & 1.0356 \cdot i \\ -1.0356 \cdot i & 1.0356 \end{bmatrix},$$

$$\text{norm}(S_{\text{MNLS}}) = 1.8531,$$

$$V_{\text{MNLS}} = \begin{bmatrix} -0.6061 \cdot i & -0.7954 \cdot i \\ 0.7954 & -0.6061 \end{bmatrix},$$

$$D_{\text{MNLS}} = \begin{bmatrix} 1.8247 & 0 \\ 0 & -0.3234 \end{bmatrix}. \quad (9a''')$$

In this case, the MNLS solution determined from this different set of partial measurements is different from that in Eq. (9a'''). It is not the true (globally optimal) solution, either. Therefore, FAT assures the overall optimal solution for system reconstruction when at least M^2 responses from the different excitations are available. In addition, FAT assures the best (local) MNLS solution at each iterative session in the reconstruction phase for an adaptive control of hyperthermia before the M^2 steps. The MNLS solution satisfies all the

incomplete information retrieved, but remains a local optimum since it is not guaranteed satisfying those missing or upcoming information.

V.A.2. Noisy partial reconstruction (NYPR)

In the presence of noise that is described by a linear system, the reconstruction of Eq. (3) remains a linear problem and is formulated below,

$$\begin{aligned} \vec{b}_{N \times 1, \text{Noisy}} &= \begin{bmatrix} A_{N \times M^2, \text{Noiseless}} & C_{N \times R} \end{bmatrix} \cdot \begin{Bmatrix} \vec{x}_{M^2 \times 1, \text{Noiseless}} \\ \vec{e}_{R \times 1} \end{Bmatrix} \\ &= A_{N \times (M^2+R), \text{Noisy}} \cdot \vec{x}_{(M^2+R) \times 1, \text{Noisy}}. \end{aligned} \quad (9b)$$

Unfortunately, the exact mathematical expression for noise is unknown in practice. Therefore, one can only formulate an approximate linear system consisting of only the noiseless matrix and vector, and then determine the best among this kind of linear system to approximate the (true) noisy linear system. This idea of approximation is also employed when the noise is produced from a nonlinear system.

To minimize the effects of the noise involved in the MRTI feedbacks, one needs to determine the LSE approximate reconstruction, i.e., projecting the image feedbacks onto the range of the linear system assembled by the driving signals, according to FAT. Next, one needs to ensure the unique MNLS reconstruction, as one would do for the NLPR. Therefore, in practice, by FAT, one must reconstruct the MNLSE approximate representative system matrix to fulfill the needs of a successful real-time image-guided hyperthermia control.

Except that only an approximate solution is retained, all other characteristics of NLPR are inherited by NYPR. Readers then have a clear idea that the key to determine the global optimal heat configuration without completing all the M^2 steps of reconstruction of the system is to supplement addition equations.

V.B. Analysis for linear learning strategy involving method of model reduction

There are multiple ways to augment equations to the system reconstruction associated with the real-time adaptive control of hyperthermia to reduce the time expenditure required to accomplish the desired spatially focused heating in tumor. One such approach is using the model reduction of VS.²⁹ The equation linking the input variables and the associated output temperature is given in Eq. (7). Based on FAT, the problem dimension is reduced from M^2 to N^2 .

In the case that only the optimality of the tumor temperature is considered [Eq. (3b)], based on MAT, the dynamics of the original (true) system are optimally and approximately preserved. The error estimate of this method of model reduction is also provided by MAT, see Eqs. (6c) and (6c'). One can choose to use other vectors to span the reduced subspace; nevertheless, based on MAT, the use of the first few orthonormal eigenvectors of the true representative matrix is the best theoretical choice among all other choices using the same number of unit vectors.

Suppose the optimal criterion that simultaneously maximizes the average tumor temperature and constrains the maximally allowable average temperature in normal tissue is used, the representative system matrix is the product of the inverse of the average normal tissue system matrix and the average tumor system matrix.⁴¹ In this case, the representative system matrix is not Hermitian, in general. As a result, the eigenvectors are not orthonormal, in general, but they remain linearly independent and can be used as basis vectors to form reduced-order VS subspace. Since the representative matrix is not Hermitian, the eigenvectors and the singular vectors of this representative system matrix are not the same. Consequently, one cannot use MAT to explicitly estimate the approximation error.

Because thermal dissipation is a slow process and one must impose multiple (M^2 or N^2) and different excitations for the applicator to produce the minimum number of MRTI feedback signals required by FAT to complete the system reconstruction, it will take intolerably long times if one waits for the elevated temperatures to fall back to initial baseline conditions. Recent studies suggested either retaining a simple model to predict the temperature decay process during the power-off period²⁴ based on the concept of effective perfusion,^{49,50,52,51} or simply take the difference of the temperature at the end of power-on period with that of at the end of the following power-off period.^{26,27} Both approaches introduced errors due to model approximation or model mismatch, and therefore, the system reconstruction problem is described by Eq. (9b). When the VS model reduction,²⁹ which was developed based on linear system theory, is employed to reduce problem complexity in the presence of temperature-dependent perfusion,^{26,27} the use of a linear model to approximate a nonlinear model also introduces model mismatch, and the analysis of the problem is again based on Eq. (9b).

Moreover, the potential time saving by using parallel computing or faster computer hardware¹⁴ would be limited when a linear learning strategy is used. The reason is that a linear learning strategy is not very complicated, and thus the slow thermal cooling required for every single pulse becomes more critical. Nevertheless, the use of parallel computing and/or faster hardware might be helpful speeding up a nonlinear learning strategy.

V.C. Comparative analysis between linear reconstruction and nonlinear reconstruction

In addition to linear reconstruction, nonlinear reconstruction is also possible. Its general mathematical expression is given in Eq. (4).

At a first glance, a linear reconstruction cannot compete with a nonlinear one, since the complexity of the former is M^2 while the later 6^*M . Nevertheless, there are certain hidden costs involved with a nonlinear reconstruction. Analysis is given here for a paper formulated a nonlinear reconstruction to solve the real-time adaptive control of hyperthermia.²⁵

FIG. 2. Iterative correction of the driving vector to heat tumor selectively and minimize heating of the surrounding normal tissue. The vertical axis denotes the dot product of the driving vector at each iterative step of system reconstruction and the optimal driving vector. Value 1 refers to the best match and 0 the worst. The horizontal axis denotes the iteration.

In 2007, an adaptive controller for hyperthermia using nonlinear reconstruction was derived by neglecting all convective and conductive heat transfer effects and the Pennes perfusion.²⁵ In that simple model, temperature distribution response becomes a rescaled power deposition. The simple model then allows them to have an explicit “temperature” expression for their nonlinear reconstruction algorithm. The Gauss–Newton (GN) algorithm incorporating with pseudoinverse⁵² was retained as the kernel device to solve this problem of nonlinear reconstruction. A limitation of that controller is that the GN algorithm demands a good initial guess to ensure its convergence. Besides, the GN algorithm requires a finite number of iterative search steps to reach convergence of one learning session, and thus it is fair to multiply an extra time delay factor onto the value of $6 \cdot M$. Unless one can theoretically prove that this additional multiplier is always less than $M/6$, the theoretical complexity of this kind of nonlinear reconstruction is not better than a linear one. Besides, the nonlinear reconstruction [see the second equality of Eq. (2a)] only identifies the E-field. But the therapeutic effects of hyperthermia concern temperature.^{53,23} To determine the optimal configuration optimizing the temperature distribution inside patient, one must use other reconstruction algorithm to obtain the *in situ* information regarding the bioheat transfer process, e.g., the values of perfusion and the velocity of blood flow. This introduces more complexity designing the adaptive controller and extra computational works for reconstruction of a system that more accurately describing the thermal physics. Even more challenging, the use of the GN algorithm demands the values of the derivatives of the temperatures inside patient to each independent variable, e.g., the phase and magnitude of each heat source. But explicit expressions for these derivatives are unavailable for BHTE. This necessitated simplifications to the BHTE, so that those derivatives can be evaluated very fast as reported.²⁵ How to maximally preserve the hyperthermia physics becomes an important concern in making one such simplification.

There are more details involved in a nonlinear scheme for system reconstruction;³⁹ however, a general structure of a nonlinear reconstruction involves formulating a nonlinear reconstruction problem and then linearizing the problem to de-

rive a specific iterative correction scheme, e.g., the GN algorithm, to determine the solution. Therefore, the analysis using FAT remains essential to understand the fundamental properties of the linearized problem. Thus, based on the conclusion drawn from the analysis given in Sec. V A, a potential approach to shorten the time expenditure of nonlinear system reconstruction could be a creative use of the method of VS reduction.²⁹

V.D. Numerical studies

Shown here are some numerical simulations exhibiting the performance of the VS-based linear adaptive control approach in a practical thigh sarcoma patient model. Both the convective cooling from blood flow and the cooling from temporally varying perfusion were included.

V.D.1. Perfusions remain constant in time

Shown here are simulations under easier conditions. In each single update session, the dynamics of the heat transfer are approximately identical. Thus, the representative system matrix does not change throughout the hyperthermia treatment.

Figure 2 shows the iterative corrections for the optimal driving vector. The driving vector is determined to maximize the average tumor temperature based on the average tumor system matrix reconstructed at each iterative step. The reconstruction was performed in the aforementioned two types of reduced-order VS subspaces. Readers also observe the fact that before the N^2 steps of iterative corrections; in general, the optimal reconstruction cannot be accomplished, as predicted by FAT. Figures 3(a) and 3(b) exhibit the temperature evolutions resulted from this adaptive control using VS partial reconstruction for the simulated two cases. The figures exhibit selective tumor temperature elevation, and thus, satisfactory treatment was accomplished based on the proposed adaptive controller following all the theoretical concerns analyzed herein.

FIG. 3. (a) Temperature evolution during the process of iterative correction of the system. The number shown in the upper right corner is the number of iteration. Temperatures across the sagittal and axial planes at selected iterative steps are shown for case 1, for which the VS basis vectors are determined from the average tumor system matrix, and the driving vector determined in each iterative step is designed to maximize the average tumor temperature. Anatomical structures are identified more easily in the axial cross-sections. The two irregular regions at the top and bottom are muscle, and surrounded by fatty tissue. The small round-shaped region in the upper middle is bone. The highest temperature region ($\geq 43^\circ\text{C}$) is the sarcoma which is seen as an almost circular region at the left. Three progressively lowered temperature regions immediately surrounding the sarcoma at $\geq 41^\circ\text{C}$, $\geq 40^\circ\text{C}$, and $\geq 39^\circ\text{C}$ each represented with different color are best shown in iteration steps 22, 26, 36, and 40. (b) Temperature evolution during the process of iterative correction of the system. The number shown in the upper right corner is the number of iteration. Temperatures of sagittal and axial planes at chosen iterative steps are shown for case 2, for which the VS basis vectors are determined from the representative system matrix being designed to simultaneously maximize the average tumor temperature and minimize the average normal tissue temperature, and the driving vector determined in each iterative step is aiming to maximize the average tumor temperature.

V.D.2. Tumor and muscle perfusions vary in time

Shown here are simulations under more complicated approximations. The dynamics of heat transfer in each single update session are not the same because the perfusions in tumor and muscle have a step change at the beginning of the eighth update session. Hence, the representative system matrices before and after this step change in perfusions are not the same.

FIG. 4. Iterative correction of the driving vector to heat tumor selectively and minimize heating of the surrounding normal tissue. The vertical axis denotes the dot product of the driving vector at each iterative step of system reconstruction and the optimal driving vector. Value 1 refers to the best match and 0 the worst. The horizontal axis denotes the iteration. The time duration of iteration is 3 min. In this figure, the perfusion values in the assigned tumor and muscle regions were increased at 24 min.

Figure 4 exhibits the updating history of optimal driving vector when the first two to four orthonormal eigenvectors of the average tumor matrix were retained to span the reduced-order subspace. Theoretically, full reconstruction reaches at the 4th, 9th and 16th iterative step, when two, three, and four VS vectors were used to build the VS subspace. Although the perfusions in tumor and part of muscle were increased at the 8th step, the optimal driving vector was still realized around the 24th step and maintained thereafter when the 4-VS subspace was used. Comparing this case with the case 1 shown in Fig. 2, one observes that the process of the iterative corrections was different because now the perfusions were suddenly increased in the cases shown in Fig. 4. Nonetheless, the steps required remained close for determining the optimal driving vector and maintaining this vector. Similarly, the optimal driving vector of the case when the 2-VS subspace was used was also maintained after being determined throughout the simulations. However, the steps required for the optimal driving vector of the case when the 3-VS subspace was used were increased to ~ 16 . This implies that the adaptive learning algorithm indeed corrected the system from the feedbacks, but it demanded a finite number of learning steps to recover the true system, when there was new perturbation. Once corrected, the algorithm seems to be stable. Figure 5 shows the dynamics of the temperature in axial and sagittal views at some selected instances. Selective tumor heating still achieved, but the tumor heating was not as good as that shown in Fig. 3. This is most likely because of the increase in tumor perfusion and the perfusions of the muscle near the tumor. Higher percentage of heated tumor region can be accomplished if more aggressive values of the parameters in the (traditional) control of total power are assigned.

FIG. 5. Temperature evolution during the process of iterative correction of the system. The number shown in the upper right corner is the number of iteration. The time duration of iteration is 3 min. Temperatures across the sagittal and axial planes at selected iterative steps are shown for case 1, for which the four VS basis vectors are determined from the average tumor system matrix, and the driving vector determined in each iterative step is designed to maximize the average tumor temperature. In this figure, the perfusion values in the assigned tumor and muscle regions were increased at 24 min.

Lastly, it is expected that more elegant and sophisticated methods will be developed for real-time MRI-guided adaptive control of hyperthermia or thermal ablative therapy. However, any adaptive control algorithm attempting to optimally reconstruct the system linearly [e.g., the representative system matrix in Eq. (3)] or nonlinearly [e.g., the E -matrix in Eq. (4)] must always satisfy the mathematical requirements of the existence and uniqueness of solution. The Fredholm alternative analysis has shown that any linear partial reconstruction method cannot guarantee determining the global optimal solution because the full information of the system is not retrieved for lacking enough equations to solve all the unknowns. One can choose a set of *a priori* patient information to provide additional equations rather than using assumptions to uniquely determine all the components of the representative system matrix.³⁹ In addition, the numerical simulations showed that although the proposed algorithm indeed recovered a good heating vector delivering selective tumor heating, a finite correction steps would be required under the simulated situation when perfusion values of tumor and some part of muscle having an abrupt increase to twice of their original values. This implies that a finite number of reupdating the system to reattain a good heating vector might be required if there is a large enough sudden perturbation on perfusion when perfusion is a function of time or temperature or both. This unpleasant consequence demands further investigations on reducing the number of correction for reattaining a good heating vector. For example, a combination of the Tikhonov-Phillips regularization as suggested in our another study³⁹ with the methods provided herein.

VI. CONCLUSIONS

The design of a real-time image-guided adaptive controller for the treatment is one of the major current research

topics in hyperthermia or thermal adaptive therapy, especially the inclusion of one such controller with a real-time three-dimensional medical imaging technique such as MRI. NLPR with the MNLS method under the assumption of simple noiseless conditions asserts timely the unique locally optimal approximate heating vector at each iterative improvement, starting from the initiation of the treatment. The NYPR method with MNLSE method asserts all the successes from the NLPR, and under the presence of practical noise. Unfortunately, this approach cannot guarantee that the optimal heating vector is globally unique until a time-consuming full reconstruction is reached. Numerical simulations for the iterative learning using noisy (simulated) MRTI feedback conducted in a human thigh sarcoma model agreed with this theoretical prediction. Hence, based on the Fredholm alternative analysis presented herein, it is clear that obtaining a unique global optimal heating vector for a multisource applicator in a clinically practical timeframe is theoretically attainable using partial reconstruction with MNLS/MNLSE method and supplemented with additional equations.

For the future, it is important to discover a quantitatively and generally applicable strategy capable of providing a reliable set of initial information to satisfy mathematical requirements of the existence and unique solution provided herein. One can choose a set of *a priori* patient information to provide additional equations rather than using assumptions to uniquely determine all the components of the representative system matrix. This should minimize the intolerably long reconstruction process of determining the unique MNLSE optimal heating vector. One such approach is to integrate the method of virtual source (VS) with the MNLSE method by assuming the true optimal driving vector is enclosed in the VS subspace of a lower dimension. When the goal of treatment is to maximize the average tumor temperature, by MAT, the optimal choice of the basis vectors to span the reduced-order subspace is the use of the first few VS basis vectors of the average tumor matrix. The applicability of this approach was confirmed by numerical simulations conducted under the conditions when convective cooling is included during hyperthermia and when there is a sudden increase in perfusion in muscle and tumor. Developing other methods to augment equations is possible and is an important future research direction.

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