Mathematical formulation and analysis of the nonlinear system reconstruction of the online image-guided adaptive control of hyperthermia

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(Received 15 April 2009; revised 21 December 2009; accepted for publication 23 December 2009; published 5 February 2010)

Purpose: A nonlinear system reconstruction can theoretically provide timely system reconstruction when designing a real-time image-guided adaptive control for multisource heating for hyperthermia. This clinical need motivates an analysis of the essential mathematical characteristics and constraints of such an approach.
Methods: The implicit function theorem (IFT), the Karush–Kuhn–Tucker (KKT) necessary condition of optimality, and the Tikhonov–Phillips regularization (TPR) were used to analyze and determine the requirements of the optimal system reconstruction. Two mutually exclusive generic approaches were analyzed to reconstruct the physical system: The traditional full reconstruction and the recently suggested partial reconstruction. Rigorous mathematical analysis based on IFT, KKT, and TPR was provided for all four possible nonlinear reconstructions: (1) Nonlinear noiseless full reconstruction, (2) nonlinear noisy full reconstruction, (3) nonlinear noiseless partial reconstruction, and (4) nonlinear noisy partial reconstruction, when a class of nonlinear formulations of system reconstruction is employed.
Results: Effective numerical algorithms for solving each of the aforementioned four nonlinear reconstructions were introduced and formal derivations and analyses were provided. The analyses revealed the necessity of adding regularization when partial reconstruction is used. Regularization provides the theoretical support for one to uniquely reconstruct the optimal system. It also helps alleviate the negative influences of unavoidable measurement noise. Both theoretical analysis and numerical examples showed the importance of having a good initial guess for accomplishing nonlinear system reconstruction.
Conclusions: Regularization is mandatory for partial reconstruction to make it well posed. The Tikhonov–Phillips regularized Gauss–Newton algorithm has nice theoretical performance for partial reconstruction of systems with and without noise. The Levenberg–Marquardt algorithm is a more robust algorithmic option compared to the Gauss–Newton algorithm for nonlinear full reconstruction. A severe limitation of nonlinear reconstruction is the time consuming calculations required for the derivatives of temperatures to unknowns. Developing a method of model reduction or implementing a parallel algorithm can resolve this. The results provided herein are applicable to hyperthermia with blood perfusion nonlinearly depending on temperature and in the presence of thermally significant blood vessels.
[DOI: 10.1118/1.3298005]

Key words: implicit function theorem, Karush–Kuhn–Tucker necessary condition of optimality, optimization, regularization, Gauss–Newton algorithm, Levenberg–Marquardt algorithm, full reconstruction, and partial reconstruction

I. BACKGROUND AND SIGNIFICANCES

Hyperthermia is a cancer treatment modality that has been shown clinically capable of enhancing the therapeutic effects of radiation[1] and/or chemotherapy[2] because of the elevated temperature it induces. Hyperthermia has received increasing attention partially because of the rapid development in medical imaging techniques. This imaging allows clinicians to obtain faster and more detailed patient information to adjust power focusing.[3–5] Consequently, tumor temperature localization is improved.

Selective heating is essential to the success of hyperthermia therapy. Only then can the tumor be maximally destroyed by spatially confined power, while the surrounding normal tissues are maximally preserved. The integrated environment of patient and heat sources is hereby referred to as the system. It is derived from physical laws and can be gradually updated by using feedback from a learning process. To realize accurate confined tumor heating, an accurate mathematical description of the system is essential. The accuracy of the system description can be degraded by many factors. For example, the tissue electric and thermal properties are usually very patient specific,[6,7] and thus there would be discrepancies between the published values and the actual values of the patient under treatment. In addition, blood perfusion that may affect the therapeutic results[8,9] can differ even for the same patient from one treatment session to another. As such, accurate patient positioning within a flexible water bolus is also difficult to be estimated before the treatment.[10] All of these uncertainties and the unavoidable noise involved in temperature feedback from a medical imaging scanner, e.g., magnetic resonance imaging (MRI) scanner, degrade the reliability of the description of a system.[8,9,11] It is clear that the success of hyperthermia therapy requires adaptation of a system control strategy that provides the most accurate dynamic patient-specific information.

The inclusion of a learning strategy distinguishes adaptive control from other control methodologies. Adaptive control of hyperthermia consists of a learning process and a feedback kernel. By using a measurement feedback, the learning process gradually improves the accuracy of the mathematical form that describes the system. The feedback kernel applies the control rules to steer the power spatially and optimally and to restrict the power within the tumor.[8,11,12] This feedback kernel also adjusts the total power output to reach and maintain the desired temperature.[13,8]

Different formulations of a system require different learning strategies. Although the measuring device and the integrated environment of a patient and heat sources involved remain the same, different computational complexities are associated with different learning strategies. This is because different system formulations have different number of independent variables and different mathematical structures to convert the same feedback information to corresponding output. The number of independent heat sources (M) plays an important role in estimating the workload of a learning strategy. To fully reconstruct the system when M independent heat sources are employed, a linear learning strategy[8] theoretically requires M^2 learning steps because its system is an M-by-M Hermitian matrix.[14] In contrast, a nonlinear learning strategy[15] requires 6^*M steps because its system consists of a 3-by-M complex matrix; the number 3 comes from the three-dimensional geometry, M is the number of independent heat sources, and each source has a complex variable that has two real components ($3^*M^*2=6^*M$). As more heat sources (for example, $M>6$) are applied to provide better spatial temperature focusing, a nonlinear learning strategy clearly becomes even more attractive than a linear strategy because it demands fewer learning steps thus shortens the time expenditure for learning. However, even when a nonlinear learning strategy is applied, it could still take long time for a complete learning process. For instance, when a patient is treated by a modern phased-array applicator like BSD-2000 Sigma-Eye heating applicator (Sigma-Eye/MR, BSD Corporation, Salt Lake City, UT) which has 12-paired antennas in three rings, it could take hours for the nonlinear learning process because it demands 72 steps of learning correction.[15] To further accelerate this learning process, a recent research direction is to explore the development of a learning strategy that only requires partial reconstruction. In particular, this strategy attempts to determine the optimal configuration of heat sources when delivering a spatially confined tumor heating before the system is fully reconstructed. Currently, partial reconstruction is addressed in the following published works,[8,15] and some approaches incorporating model reduction were developed recently.[11,12]

There are certain theoretical limitations regarding the development of a successful partial reconstruction approach using a nonlinear learning strategy, but there is no formal theoretical analysis highlighting and addressing them. Therefore, the authors were motivated to analyze and emphasize those theoretical considerations and provide solutions to address these issues. This paper will describe and analyze algorithms for nonlinear full and partial reconstructions using feedback with unavoidable noise. Rigorous theoretical support will also be provided for these algorithms. Problem formulation and mathematical analysis will be conducted for problems with increasing theoretical complexity: From the problem of nonlinear full reconstruction using noiseless feedbacks to nonlinear partial reconstruction using noisy feedbacks. After completing the formulation and analysis for hyperthermia described by linear physical model with constant parameters, the analysis will be conducted for more practical and complicated conditions of hyperthermia with blood perfusion nonlinearly varying with temperature. Lastly, numerical exhibitions will be given, followed by comparisons between nonlinear and linear formulations of system reconstruction.

II. METHODS FOR THEORETICAL ANALYSIS AND NUMERICAL EXHIBITION

Theoretical descriptions of the physical processes related to the design for real-time image-guided control of hyperthermia are first provided. Then followed are mathematical theorems and the related numerical setups for the purpose of illustrations.

II.A. Governing equations for the thermal and wave physics

Using a set of externally applied nonionizing heat sources, the internal temperature of human body is locally elevated to a therapeutic level and is maintained for a treatment period to deliver a lethal thermal dose to the target cancerous cells. This kind of treatment is called multisource loco regional hyperthermia. Assuming that the bioheat transfer (BHT) process inside human body is linear, the temperature response to a given power deposition is written below,[8]

$$T(t,\vec{r}) = \int_{\tau=0}^{t} \int_{V'} G(t-\tau,\vec{r}-\vec{r}\,') \cdot P_{\text{sum}}(\tau,\vec{r}\,') \cdot dV' \cdot d\tau. \tag{2.1}$$

Here, the scalar t is time, and the vector r is a function of the x, y, and z variables indicating the spatial position. The function G is called Green's function,[16–19] and P_{sum} denotes the power deposition delivered by a set of nonionizing sources.

Zero initial and boundary conditions are assumed here to simplify further analysis. The Green's function is a compact expression representing the response of a linear system to an impulsive input. The Green's function exists regardless of whether the linear problem formulation is time invariant or varying,[16] and whether the domain of the problem is finite or infinite, regular or irregular.[17–19] The Green's function here implicitly includes the effects of thermal properties of the patient and the position of the tumor relative to the patient and the applicator, etc.

There are two types of commonly employed nonionizing sources: Electromagnetic (EM) waves and ultrasonic (US) waves. Richer technical issues are contained in the case when EM sources are used than when US sources are used. Therefore, the analysis is based on the use of EM sources; the analysis can be easily reduced to the case when US sources are used.

Assuming wave propagation inside the human body is also linear by neglecting the cross-talking and mutual coupling between sources,[20] the resultant power deposition is a function of the product of the conjugate of the synthesized electric field (E field) with itself,

$$P_{\mathrm{sum}}(t,\vec{r}) = \frac{\sigma}{2}\cdot \vec{E}^{H}_{\mathrm{sum}}\cdot \vec{E}_{\mathrm{sum}}, \quad \vec{r}=(x,y,z). \tag{2.2}$$

Here, the superscript H denotes the complex conjugate transpose, and σ is the electric conductivity.

Based on linearity assumption of the wave propagation, the resultant E field is given by the following equation:

$$\vec{E}_{\mathrm{sum},3\times 1}(t,\vec{r}) = \sum_{m=1}^{M} \vec{E}_{m,3\times 1}\cdot u_m = E_{3\times M}(t,\vec{r})\cdot \vec{u}_{M\times 1}(t). \tag{2.3}$$

Here, M is the number of antennas, the vector E_m denotes the E field from antenna m, and u_m refers to the mth (complex) antenna configuration.

A controller is required for hyperthermia to generate a power deposition that selectively elevates tumor temperature and to avoid undesired hot spots in normal tissues, which would cause damage, patient pain, or discomfort. Given below are theories related to the design for the control of hyperthermia.

II.B. The design for control of BHT process

It is desirable to obtain a formulation explicitly linking together the clinical outputs (temperatures) and the control variables (the driving vector of the heating sources). For simplicity, the derivation assumes that power does not change continuously in time. Therefore, the equations in Sec. II A are simplified and combined to provide one such equation below,

$$T(t,\vec{r}) = \vec{u}^{H}\cdot\left(\frac{\sigma}{2}\cdot\int_{\tau=0}^{t}\int_{V'} G(t-\tau,\vec{r}-\vec{r}\,')\cdot (E^{H}_{M\times 3}\cdot E_{3\times M}(\vec{r}\,'))\cdot dV'\cdot d\tau\right)\cdot \vec{u}. \tag{2.4}$$

The terms in the parentheses together represent the system, the vector u denotes the driving vector to the heat sources, and T is the output temperature. With this equation, one can proceed to design a controller that adjusts the components of the driving vector so that the corresponding temperature response satisfies the goal of hyperthermia.

A complicated mathematical model more accurately describes the underlying physics. However, a simpler model better serves the purpose of numerically demonstrating the essential theoretical characteristics of the design for a nonlinear learning strategy associated with online image-guided control of hyperthermia. Therefore, a simpler model approximately describing the clinical physics involved is also given here,

$$\rho\cdot C_t\cdot\frac{dT}{dt} = -w_b\cdot C_b\cdot T + \frac{\sigma}{2}\cdot\vec{u}^{H}\cdot(E^{H}_{M\times 3}\cdot E_{3\times M})\cdot\vec{u}$$

$$\Rightarrow \frac{dT}{dt} = -\beta\cdot T + \frac{\sigma}{2\cdot\rho\cdot C_t}\cdot\vec{u}^{H}\cdot(E^{H}_{M\times 3}\cdot E_{3\times M})\cdot\vec{u}$$

$$\Rightarrow T(t,\vec{r}) = T(0,\vec{r})\cdot\exp(-\beta\cdot t) + \frac{\sigma}{2\cdot\beta\cdot\rho\cdot C_t}\cdot\vec{u}^{H}\cdot(E^{H}_{M\times 3}\cdot E_{3\times M})\cdot\vec{u}\cdot(1-\exp(-\beta\cdot t)). \tag{2.5}$$

Here, ρ is tissue density, C_t is the specific heat of tissue, w_b indicates the Pennes perfusion,[21] β is the effective perfusion frequency,[22] and C_b refers to the specific heat of blood. The effective perfusion frequency approximately describes the integrated local cooling from the Pennes blood perfusion[21] and thermal conduction at a point inside the patient underwent hyperthermia.[23] Hence, the important physical cooling factors known to have significant impacts on hyperthermia[24] are preserved.

II.B.1. The basic ideas of nonlinear learning strategy

The goal of a learning strategy is to optimally reconstruct the system. Therefore, in this case, the temperature (e.g., from image feedback) and the driving vector in Eq. (2.1) are given information, and the goal is to determine the ensemble of the E fields. The unknowns involved in the ensemble of the E fields are identified from the information retrieved. In Sec. III the essential features of nonlinear system reconstruction will be analyzed.

There are some essential theorems involved in optimal reconstruction of the system. First described below is the implicit function theorem (IFT).[25,26] It provides the sufficient conditions required to ensure the existence of a unique solution to a nonlinear reconstruction. Then the Karush–Kuhn–Tucker (KKT) necessary condition of optimality[27] is introduced to provide the necessary condition employed to determine the optimal solution for a given optimization problem.

II.C. The IFT

IFT is a tool that allows relations to be converted to functions. The theorem states that if the equation $R(x,y)=0$ (an implicit function) satisfies some mild conditions on its partial derivatives, then, in principle, one can solve this equation for y, at least over some small interval. Geometrically, the locus defined by $R(x,y)=0$ will overlap locally with the graph of an explicit function $y=f(x)$.

The theorem is described below using a simple case involving only a few variables and parameters; however, it can be extended to cases involving more variables and or parameters.

Let $\vec{f}:R^3\to R^2$ be a continuous differentiable (vector-valued) function in two dimensions. Assuming there is a point $(x_a,y_{b,1},y_{b,2})$ that satisfies a unique (vector) relation $\vec{g}:R\to R^2$ in two dimensions that works around the neighborhood of this point $(x_a,y_{b,1},y_{b,2})$ as long as the Jacobian is nonsingular at this point. This function g relates the variables x, y_1, and y_2 as $y_{b,1}=g_1(x)$ and $y_{b,2}=g_2(x)$. The Jacobian is given below,

$$J(x_a,y_{b,1},y_{b,2})=\begin{bmatrix}\dfrac{\partial f_1}{\partial y_1}(x_a,y_{b,1},y_{b,2}) & \dfrac{\partial f_1}{\partial y_2}(x_a,y_{b,1},y_{b,2})\\ \dfrac{\partial f_2}{\partial y_1}(x_a,y_{b,1},y_{b,2}) & \dfrac{\partial f_2}{\partial y_2}(x_a,y_{b,1},y_{b,2})\end{bmatrix}. \tag{2.6}$$

As shown in the examples below, IFT provides sufficient conditions that ensure the existence of the unique reconstruction regardless the formulation is linear or nonlinear.

II.C.1. Example II.C.1

A famous example in multivariable calculus is given here to show the power of IFT. This is a two-dimensional coordinate transformation between the Cartesian coordinates (x,y) and the polar coordinates (r,θ).

$$\begin{cases} f_1=x-r\cos\theta=0\\ f_2=y-r\sin\theta=0\end{cases} \Rightarrow J=\begin{bmatrix}\dfrac{\partial f_1}{\partial r} & \dfrac{\partial f_1}{\partial \theta}\\ \dfrac{\partial f_2}{\partial r} & \dfrac{\partial f_2}{\partial \theta}\end{bmatrix}=\begin{bmatrix}-\cos\theta & r\sin\theta\\ -\sin\theta & -r\cos\theta\end{bmatrix}\Rightarrow \det(J)=r. \tag{2.7}$$

The IFT requires the Jacobian to be nonsingular, i.e., its determinant is nonzero. According to Eq. (2.7), this demands the value r to be nonzero. When this is the case, there is a unique coordinate transformation between the Cartesian coordinates (x,y) and the polar coordinates (r,θ). However, when $r=0$, which means IFT is violated, and then there is no such coordinates transformation.

Rewriting the IFT less formally in nontechnical terms for the current hyperthermia issue of multisource heating applicator system reconstruction, it states that when there are M unknowns, one must have M different equations that satisfy certain conditions imposed by Eq. (2.6) so that a unique full reconstruction can be ensured.

However, using the IFT alone is insufficient to handle the practical situations in the presence of unavoidable noise. Since the goal of this paper is to analyze and design a system reconstruction algorithm to expedite the learning process, together it leads to the employment of the theorem regarding to the numerical optimization. Next, the KKT necessary condition of optimality is introduced. Based on this condition, one can better analyze and design a full or a partial reconstruction algorithm to expedite the learning process for the real-time adaptive control of hyperthermia involving unavoidable noise.

II.D. The Karush–Kuhn–Tucker (KKT) necessary condition of optimality

The KKT conditions are necessary for a solution in nonlinear programming to be optimal, provided some regularity conditions are satisfied. This condition is written below. Given an unconstrained quadratic optimization problem, the optimal solution is a critical point of the objective function and hence its gradient equals to zero,

$$\min_{\vec{x}_{M\times 1}} g(\vec{x}_{M\times 1})=\min_{\vec{x}_{M\times 1}}\tfrac{1}{2}\cdot\|\vec{f}_{N\times 1}(\vec{x}_{M\times 1})\|_2^2. \tag{2.8}$$

Here, the real scalar function g, which is the half of the square of the Euclidean norm of the vector function of f, is called the objective function, goal function, or criterion function. The vector function of f has N different components. Each component of the vector function f denotes the difference between the measured and the predicted outputs from a given excitation. In hyperthermia, this output can be a vector in which each of its elements is a product of a selected weighting coefficient and temperature at a point of interest.[9] The points of interest could be tumor points only[8,9] or include the points in critical normal tissues.[13,15] The KKT necessary condition indicates that the optimal solution satisfies the following conditions:

$$\frac{\partial g}{\partial \vec{x}_{M\times 1}} = \vec{0}_{M\times 1} = J^A(\vec{f}_{N\times 1},\vec{x}^A_{1\times M}) \cdot \vec{f}_{N\times 1}(\vec{x}_{M\times 1}). \quad (2.9)$$

The superscript A denotes complex conjugate transpose for complex variable and transpose for real variable. The first term (J) in the right side of the equality is called the Jacobian, which denotes the gradient of a vector function.

II.E. Configurations for numerical simulations

It is difficult to understand all the properties of the models purely based on the aforementioned advanced mathematical theorems. Thus, commercial software MATLAB™ (The MathWorks, Inc., Natick, MA) was used to conduct numerical experiments to explicitly illustrate the results analyzed using the abstract theorems.

The approximate physical model expressed by Eq. (2.5) was used for the aforementioned purpose, but zero initial temperature was assumed for simplicity. It was also assumed that there are only three point sources. The target of heating was the coordinate origin, and the coordinates of the three sources were (11.5, 0, 0), (0, −11.5, 0), and (−11.5, 0, 0); the unit of the coordinates was centimeter. Note the dimensions of this simulation configuration were used to mimic a design of 10-antenna cylindrical applicator for hyperthermic treatment of extremities that was used in previous studies.[9,12] The heating period was 5 min for each single power excitation that was used to produce temperature feedback. Thermal interactions between different excitations were assumed to be negligible to simplify the analysis. The electric and thermal property values[28,29,7,30,31] involved for the numerical demonstrations were given as those for (human) muscle when the driving frequency of the EM wave was 150 MHz. The electric permittivity was $5.507\,188\times 10^{-10}$ F/m, the electrical conductivity was 0.727 S/m, the permeability was $4^*\pi^*10^{-7}$ H/m, the density was 1050 kg/m^3, the specific heat of muscle was 3639 J/kg K, the specific heat for blood was 3770 J/kg K, and the blood perfusion was 3.6 kg/m^3 s.

III. ANALYZED RESULTS AND DISCUSSION

In the following sections, effective algorithms and limitations for four different types of nonlinear reconstruction are analyzed, including the combinations of full and partial reconstructions, and noiseless and noisy situations. Then discussions and comparisons with a previously published algorithm[15] are given, followed by an analysis for nonlinear system reconstruction of adaptive control of hyperthermia when the perfusion is nonlinearly temperature dependent. Numerical exhibitions are also presented. Then, comparisons between nonlinear and linear reconstructions are provided.

III.A. Nonlinear noiseless full reconstruction (NNLFR)

A full reconstruction in the absence of noise is first demonstrated using a numerical optimization. The optimization problem is formulated as in Eq. (2.8). Based on the KKT necessary optimality condition given in Eq. (2.9), the optimal system reconstructed can be determined by the following implicit equations:

$$\vec{0}_{6\cdot M\times 1} = \vec{h}_{6\cdot M\times 1} \triangleq J^A(\vec{f}_{6\cdot M\times 1},\vec{x}^A_{1\times 6\cdot M}) \cdot \vec{f}_{6\cdot M\times 1}(\vec{x}_{6\cdot M\times 1}). \quad (3.1)$$

Unfortunately, Eq. (3.1) is also a system of nonlinear equations. Since generally there is no closed-form solution to a nonlinear problem, among many algorithms, the Gauss–Newton (GN) algorithm[32,33] is chosen to solve Eq. (3.1). This method is well known and provides an ideal convergence rate of second order.

The basic idea of this algorithm is to first approximate the vector function h by the Taylor expansion. A hypothesis associated with this expansion is that the two consecutive points at the levels of k and $(k+1)$ iterative corrections are close enough,

$$\vec{0}_{6\cdot M\times 1} \approx \vec{h}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}) + (R_{6\cdot M\times 6\cdot M}(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k)}_{6\cdot M\times 1}) + J^A\cdot J(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M}))\cdot(\vec{x}^{(k+1)}_{6\cdot M\times 1} - \vec{x}^{(k)}_{6\cdot M\times 1}). \quad (3.2)$$

By neglecting the high order term described by the matrix R, the following algorithm is developed:

$$\vec{x}^{(k+1)}_{6\cdot M\times 1} = \vec{x}^{(k)}_{6\cdot M\times 1} - (J^A\cdot J(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M}))^{-1} \cdot \vec{h}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}). \quad (3.3)$$

If converged, Eq. (3.3) gives the optimal solution to the optimal reconstruction problem and thus one has the system reconstructed. Nevertheless, as shown in the IFT, there might not be a unique solution or even any solution to the KKT condition given in Eq. (3.1). To obtain the conditions for the existence and uniqueness of the solution to Eq. (3.3), the following analysis is conducted:

$$\frac{\partial \vec{h}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1})}{\partial \vec{x}^{(k),A}_{1\times 6\cdot M}} = R_{6\cdot M\times 6\cdot M}(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k)}_{6\cdot M\times 1}) + J^A\cdot J(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M}). \quad (3.4)$$

Here, the matrix R denotes a collection of all the high order terms. Based on IFT, the above matrix is required to be nonsingular to ensure that the solution exists and is unique. Therefore, according to Eqs. (3.3) and (3.4), the neglect of the high order terms represented by the matrix R does not devoid the sufficient condition imposed by IFT to ensure the existence of the unique solution to the optimal reconstruction problem.

The GN algorithm is a method belonging to the family of Newton methods, and thus a good initial guess must be supplied for this algorithm; otherwise this algorithm will not converge to the correct solution. In addition, the success of linearization [from Eqs. (3.2) and (3.3)] relies on the fact that the correcting vector Δx is small. The correcting vector at the iterative step k is demonstrated below,

$$\Delta\vec{x}^{(k)}_{6\cdot M\times 1}=\vec{x}^{(k+1)}_{6\cdot M\times 1}-\vec{x}^{(k)}_{6\cdot M\times 1}. \quad (3.5)$$

This requirement of small correcting vector might be violated during iteration since there is no restriction on the magnitude of this correcting vector from the GN algorithm. As a result, the objective function my increase from one iteration step to another.[34,35] Besides, the Jacobian matrix in Eq. (3.3) could temporarily become singular during the iterative search and thus halt the GN algorithm before convergence.[34,35] In the presence of noise from image feedback, the discrepancy between the measured and the predicted vector function f could become worse than a noiseless one, which, in turn, results in a poorer behavior of its gradient, the elements of the Jacobian matrix. This further increases the chance of making the Jacobian being singular during the GN search process. These issues are addressed in the following.

III.B. Nonlinear noisy full reconstruction (NNYFR)

In the presence of noise, the goal is to find the best approximate solution to the nonlinear reconstruction. In this case, again based on the IFT and the derivation for the GN algorithm, in order to iteratively solve the KKT necessary optimality condition, 6^*M different excitations are required to fully reconstruct the approximate system; different in the sense that the requirements of IFT are fulfilled.

As mentioned in Sec. III A, the Jacobian of Eq. (3.3) could become singular when the correcting vector Δx is too large.[34,35] A remedial approach is determining the optimal solution to the formulation below,

$$\min_{\Delta\vec{x}^{(k)}_{6\cdot M\times 1}} g_{\mathrm{LM}}(\vec{x}^{(k)}_{6\cdot M\times 1},\Delta\vec{x}^{(k)}_{6\cdot M\times 1})=\min_{\Delta\vec{x}^{(k)}_{6\cdot M\times 1}}\tfrac{1}{2}\cdot\|\vec{f}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1})+J_{6\cdot M\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M})\cdot\Delta\vec{x}^{(k)}_{6\cdot M\times 1}\|_2^2,$$

$$\Delta\vec{x}^{(k)}_{6\cdot M\times 1}=\vec{x}^{(k+1)}_{6\cdot M\times 1}-\vec{x}^{(k)}_{6\cdot M\times 1},\quad \|\Delta\vec{x}^{(k)}_{6\cdot M\times 1}\|_2<\delta,\quad \delta>0. \quad (3.6)$$

The optimal solution of the problem listed above is determined by solving the KKT condition of the constrained optimization above using the method of Lagrange,

$$\frac{\partial g_{LM}}{\partial\Delta\vec{x}^{(k)}_{6\cdot M\times 1}}=\vec{0}_{6\cdot M\times 1}=\frac{1}{2}\cdot\frac{\partial}{\partial\Delta\vec{x}^{(k)}_{6\cdot M\times 1}}(\|\vec{f}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}) + J_{6\cdot M\times 6\cdot M}(\vec{f}_{6\cdot M\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M})\cdot\Delta\vec{x}^{(k)}_{6\cdot M\times 1}\|_2^2 + \lambda\cdot\|\Delta\vec{x}^{(k)}_{6\cdot M\times 1}-\delta\|_2^2),\quad \lambda>0. \quad (3.7)$$

The optimal correction vector is given below,

$$\vec{0}_{6\cdot M\times 1}=(J^A\cdot J(\vec{f}^{(k)}_{6\cdot M\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M})+\lambda\cdot I_{6\cdot M\times 6\cdot M})\cdot\Delta\vec{x}^{(k)}_{6\cdot M\times 1} + \vec{h}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}). \quad (3.8)$$

Once the correcting vector for the vector x is determined, another correction is conducted at the newly updated vector. This process is repeated until convergence. This algorithm was called the Levenberg–Marquardt (LM) algorithm. It is a variant of the GN algorithm.

The LM algorithm was developed to improve the performance of the iterative correction provided by the GN algorithm by imposing additional constraint on the norm of the correcting vector at each iteration step since the linearization employed by the GN algorithm is invalid if the correction at each step is too large. As an accompanied benefit, one immediately finds that the LM algorithm will not halt when the Jacobian matrix is temporarily singular because of the newly added λ term. The value of λ changes with iterations. A general guideline is to use a larger value at the beginning of the iteration and then gradually decreases it, e.g., at a rate of exponential function. However, the λ value at the next iteration is increased if the decrease in the objective function value does not meet the imposed criterion.

An essential limitation of full reconstruction is that the time for a system reconstruction would be impractically long when a modern heating applicator like BSD-2000 Sigma-Eye applicator[36] is retained for more spatially selective and flexible temperature focusing. There are 12 pairs of dipole antennas, mounted on three rings along its longitude, four pairs on each ring. It would demand about 216 min for full system reconstruction, even when each single reconstruction session takes only 3 min. This stimulated the investigation of partial reconstruction.

III.C. Nonlinear noiseless partial reconstruction (NNLPR)

To meet clinical requirements, the goal is to find, if possible, the best solution to the nonlinear system reconstruction in a timely manner. This motivated the investigation of the possibility to find the best solution without completing the full system reconstruction, i.e., the research for the applicability of the partial reconstruction.[8,11,12,15] Because there are more unknowns than equations in this approach, some unknowns become "free variables." This means that there are infinite feasible solutions. As a result, different numerical search algorithms might converge to different system reconstructions. Moreover, the quality of the reconstructed system, as well as the quality of the optimal heating vector determined from this system, is not ensured since there is no control on the free variables.

Besides, when developing the GN algorithm in Sec. III A, the matrix R must vanish in Eq. (3.2) so that a linear recursive formulation is obtained to iteratively determine the solution until convergence. However, this means that this matrix R in Eq. (3.4) also vanishes. On the other hand, based on the IFT, a nonsingular matrix in Eq. (3.4) must present as a sufficient condition for the unique solution to exist. Since the R matrix vanishes in Eq. (3.4) and the number N (the number of equations available) is also smaller than the number 6^*M (the number of unknowns), the only remaining term in Eq. (3.4) is a singular matrix. Hence, according to IFT, whether a solution exists or is unique cannot be assured. The LM algorithm is slightly better than the GN algorithm in this regard. Because of the presence of the λ term, based on the IFT, the unique solution to the problem formulated by Eq. (3.6) can still by determined provided a good initial guess that is close enough to this optimal solution is supplemented. Nevertheless, the modified constrained optimization expressed by Eq. (3.6) is only an approximation to the desired optimization problem formulated by Eq. (2.8). Thus, owing to the presence of uncontrolled free variables, as indicated at the beginning of this section, the original reconstruction cannot be sure to have a unique optimal solution nor can be sure to its companied approximated formulation.

When a given problem does not have a unique solution, it is called ill posed.[37] There is a family of approaches called regularization methods[38,39] designed to provide an approximate solution to ill posed problem. The (regularized) optimization formulation is shown below,

$$\min_{\vec{x}_{M\times 1},\lambda>0} g_\lambda(\vec{x}_{M\times 1}) = \min_{\vec{x}_{M\times 1},\lambda>0} \tfrac{1}{2}\cdot(\|\vec{f}_{N\times 1}(\vec{x}_{M\times 1})\|_2^2 + \lambda\cdot\|\vec{x}_{M\times 1}\|_2^2). \tag{3.9}$$

The new term is called a regularization term, and λ denotes the regularization parameter. Since Tikhonov and Phillips are the major pioneers developing this kind of approach, it is denoted here as the Tikhonov–Phillips regularization (TPR).

After adding this term, the KKT necessary condition is expressed by the following equation, which is similar to Eq. (3.1):

$$\frac{\partial g_\lambda}{\partial \vec{x}_{6\cdot M\times 1}} = \vec{0}_{6\cdot M\times 1} = \vec{h}_{\lambda,6\cdot M\times 1} \triangleq J^A_{6\cdot M\times N}(\vec{f}_{N\times 1},\vec{x}^A_{1\times 6\cdot M})\cdot\vec{f}_{N\times 1}(\vec{x}_{6\cdot M\times 1}) + \lambda\cdot\vec{x}_{6\cdot M\times 1}. \tag{3.10}$$

Again the sufficient conditions need to be developed to ensure the existence of the unique solution to Eq. (3.10) according to the IFT. Note that the regularized objective function, g_λ, and its first derivative, h_λ, are different from those listed in Eqs. (2.7) and (3.1). Similar to Eq. (3.4), these conditions are provided below,

$$\frac{\partial\vec{h}_{\lambda,6\cdot M\times 1}(\vec{x}_{6\cdot M\times 1})}{\partial\vec{x}^A_{1\times 6\cdot M}} = R_{\lambda,6\cdot M\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}_{6\cdot M\times 1}) + J^A_{6\cdot M\times N}\cdot J_{N\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}^A_{1\times 6\cdot M}) + \lambda\cdot I_{6\cdot M\times 6\cdot M}. \tag{3.11}$$

The last term is always nonsingular, and thus the sufficient conditions required by the IFT can be satisfied by assigning an appropriate λ value. Nevertheless, in contrast to Eq. (2.8), now one is optimizing two competing goals simultaneously: Optimally satisfying the physical criterion described by the vector function f and minimizing the Euclidean norm of the solution. A large λ value places more weight on minimizing the norm of the solution, while sacrificing the optimality of the physical criterion.

Having the uniqueness of the optimal solution theoretically guaranteed, now it makes sense to find an efficient numerical algorithm to determine this solution. Again, the GN algorithm is analyzed first to check if it would satisfy the need herein. Equation (3.10) is linearized to get the following equations:

$$\vec{x}^{(k+1)}_{6\cdot M\times 1} = \vec{x}^{(k)}_{6\cdot M\times 1} - (J^A_{6\cdot M\times N}\cdot J_{N\times 6\cdot M}(\vec{f}^{(k)}_{N\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M}) + \lambda\cdot I_{6\cdot M\times 6\cdot M})^{-1}\cdot\vec{h}_{\lambda,6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}). \tag{3.12}$$

The algorithm above simultaneously satisfies the requirements based on the IFT and linearization required to develop the GN algorithm. It is denoted as the Tikhonov–Phillips Regularized Gauss–Newton (TPRGN) algorithm since it is an algorithm based on the idea of GN algorithm and is designed to solve a TPR problem. This algorithm allows one to iteratively determine the best system reconstructed as long as a good initial guess is supplemented with the algorithm to allow convergence. A good initial guess remains important for the convergence of this algorithm since its kernel is still the GN algorithm. In addition, the regularization term listed in Eq. (3.9) plays a role in limiting the magnitude of the correcting vector. Hence, the advantages provided by the LM algorithm mentioned in Sec. III B are also inherited here. Nevertheless, one cannot reduce the value of λ to be identically zero when the TPRGN algorithm is used to solve a partial reconstruction. Otherwise, one does not have a well-posed formulation that has a unique solution.

A seemly weakness is that the presence of a nonzero regularization term never allows one to obtain an unperturbed solution to the original system. More details addressing this will be provided in Sec. III D.

III.D. Nonlinear noisy partial reconstruction (NNYPR)

Noise is now reintroduced into the system in order to mimic the clinical situation. First, instead of using the GN algorithm developed in Sec. III A, the TPRGN algorithm developed in Sec. III C is retained to determine the unique and best approximate solution to the target nonlinear system reconstruction. Meanwhile, additional modifications are made here to better cope with the noise,

$$\min_{\vec{x}_{M\times 1},\lambda>0} g_{\lambda,W}(\vec{x}_{M\times 1}) = \min_{\vec{x}_{M\times 1},\lambda>0} \frac{1}{2}\cdot(\|\vec{f}_{N\times 1}(\vec{x}_{M\times 1})\|_2^2 + \lambda\cdot\|\vec{x}_{M\times 1} - \vec{x}_{\text{guessed},M\times 1}\|_W^2), \quad \|\vec{x}_{M\times 1} - \vec{x}_{\text{guessed},M\times 1}\|_W^2 = \vec{y}^A_{1\times M}\cdot W_{M\times M}\cdot \vec{y}_{M\times 1}, \vec{y}_{M\times 1} = \vec{x}_{M\times 1} - \vec{x}_{\text{guessed},M\times 1}. \quad (3.13)$$

Here, the vector x_{guessed} is what one guesses, based on all available physical knowledge, to be close to the true system, and the matrix W is a positive definite matrix. To make it clearer, W could be a diagonal matrix having positive elements with values set according to one's confidence with the guessed vector x. When an element of guessed vector x is found with more confidence, one can assign larger value to the corresponding element of W.

By assigning the values of the regularization parameters, one can determine the optimally reconstructed system to be the one that is closer to a guessed system. That is, this more complicated formulation allows one to utilize *a priori* information regarding the system to be reconstructed to accelerate the convergence of the iterative optimal search and to determine an optimal system that better matches the *a priori* information. Otherwise, according to previous analysis based on the IFT, theoretically one can only determine the approximated system optimally after at least 6^*M steps, when there are M independent heat sources, and when a nonlinear formulation like Eq. (2.4) is the target of reconstruction. Note, in the presence of noise in which one does not have an explicit mathematical formulation, the true system can only be recovered approximately.

In addition, the presence of noise in the image feedback contained in the vector function f makes this function noisy. Thus, it does not make much sense to formulate an optimal reconstruction problem that exactly matches the noisy responses. Instead, one ought to include as much *a priori* information based on know physics in the problem formulation so that the system reconstructed better describes the desired physics. Taking this into account, the TPRGN becomes an appealing algorithm having better theoretical properties for adaptive control of clinical hyperthermia.

Furthermore, there are different rules for assigning the value of the regularization parameter. Some popular methods for determining the λ value of a given problem are the L-curve method,[40] the cross validation method,[41] and the discrepancy principle.[42] In general, there is usually an optimal value of the regularization parameter to a given problem: A large λ value emphasizes too much on minimizing the norm of the solution at the expense of poorly matching the measured and simulated system output; however, a small λ value emphasizes too much on fitting the noisy measurement. Determining an optimal λ value to a particular regularization problem remains an active research topic.

III.E. Analysis for the PIGN algorithm

In this section, the IFT and KKT necessary conditions of optimality are applied to analyze the pseudoinverse-based GN algorithm (PIGN), which was used in the study of real-time image-guided adaptive control of hyperthermia.[15] This PIGN algorithm applied the linearization used in the GN algorithm; however, the use of the GN algorithm implies that one attempts to solve the linearized version of the KKT necessary condition of optimality described below,

$$J^A_{6\cdot M\times N}\cdot J_{N\times 6\cdot M}(\vec{f}^{(k)}_{N\times 1},\vec{x}^A_{1\times 6\cdot M})\cdot(\vec{x}^{(k+1)}_{6\cdot M\times 1} - \vec{x}^{(k)}_{6\cdot M\times 1}) = -\vec{h}_{6\cdot M\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}). \quad (3.14)$$

As a result, the iteration stops because $N<6^*M$ in NNLPR or NNYPR, and thus there is no inverse of the product of the adjoint of the Jacobian and itself. To resolve this issue, the PIGN algorithm retained the pseudoinverse[43,44] of the Jacobian to determine the unique minimum-norm least-squares error (MNLSE) approximation to Eq. (3.14). Among all corrections for this particular iterative step, this pseudoinverse correction produces optimal result in the sense that the Euclidean norm of this MNLSE correction is minimal. Using this trick, the initial guess is iteratively updated until it converges to the nonlinear equations for the KKT necessary condition of optimality (to the original optimization problem.)

However, based on the analysis accomplished in Sec. III C, the sufficient conditions for the existence of a unique solution fulfilling the KKT necessary condition of optimality are violated when the GN algorithm is used for a partial reconstruction. Consequently, the solution obtained by the PIGN algorithm might correspond to an inflection point, a local optimal solution, or the true optimal solution, if it indeed converges. Hence, in principle, one must determine all the solutions satisfying the KKT necessary condition, and then compare each of them to find the unique solution to the minimum value of the proposed objective function. However, as just stated, there might be infinite feasible solutions satisfying the KKT necessary condition due to insufficient equations, since N could be $<6^*M$ in NNLPR or NNYPR.

The IFT provides only sufficient conditions, and violating the conditions does not exclude the possibility for a unique solution of the original optimal reconstruction problem to exist. Hence, there might still be only one solution to the KKT necessary condition. For any given case, there is nevertheless no guarantee on the uniqueness of the optimal solution. Finally, the PIGN algorithm cannot guarantee the global optimal solution within 6^*M steps of full reconstruction. Unlike the TPRGN algorithm, the PIGN algorithm cannot incorporate any *a priori* physical information into the solution reconstructed. The best the PIGN algorithm can determine is the MNLSE approximation that satisfies the partial information already retrieved, i.e., a local optimum to NNYPR, in general. The approximate solution determined by TPRGN is also a local optimal in general; however, as just mentioned, by incorporating with an appropriate regularization term in Eq. (3.14), this solution might be a better approximation to the global optimal solution.

The following paragraphs show explicitly why the best the PIGN algorithm can determine is the MNLSE approximation. When developing an iterative algorithm solving nonlinear problems, a basic test is to check if a consistent result is accomplished for the companied linear problem. For this purpose, the derivation of the PIGN algorithm based on the optimization theory is given below,

$$\min_{\Delta\vec{x}^{(k)}_{6\cdot M\times 1},\lambda>0} q(\Delta\vec{x}^{(k)}_{6\cdot M\times 1}) = \frac{1}{2}\cdot \lim_{\substack{\lambda\to 0\\ ,\lambda>0}} \min_{\Delta\vec{x}^{(k)}_{6\cdot M\times 1}} \left(\begin{array}{l} \|\vec{f}_{N\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}) + J_{N\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M})\cdot \Delta\vec{x}^{(k)}_{6\cdot M\times 1}\|_2^2 \\ +\lambda\cdot \|\Delta\vec{x}^{(k)}_{6\cdot M\times 1}\|_2^2 \end{array}\right). \quad (3.15)$$

The equation above explicitly exhibits why the PIGN solution is the MNLSE approximation, in the best case. By definition, an MNLSE solution is the solution of the limiting case of a regularized optimization problem when the Euclidean norm of the solution is constrained. This formulation leads to the PIGN algorithm below,

$$\vec{x}^{(k+1)}_{6\cdot M\times 1} = \vec{x}^{(k)}_{6\cdot M\times 1} - \mathrm{pinv}(J_{N\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}^{(k),A}_{1\times 6\cdot M})) \cdot \vec{f}_{N\times 1}(\vec{x}^{(k)}_{6\cdot M\times 1}). \quad (3.16)$$

When the PIGN algorithm is used to solve a linear problem described below,

$$\vec{f}_{N\times 1}(\vec{x}_{6\cdot M\times 1}) = A_{N\times 6\cdot M}\cdot \vec{x}_{6\cdot M\times 1} - \vec{b}_{N\times 1}$$

$$\Rightarrow J_{N\times 6\cdot M}(\vec{f}_{N\times 1},\vec{x}^{A}_{1\times 6\cdot M}) = A_{N\times 6\cdot M} \quad (3.17)$$

by substituting Eq. (3.17) into Eq. (3.16), the PIGN algorithm results in the following equality and inequality:

$$\vec{x}^{(k+1)}_{6\cdot M\times 1} = \vec{x}^{(k)}_{6\cdot M\times 1} - \mathrm{pinv}(A_{N\times 6\cdot M})\cdot (A_{N\times 6\cdot M}\cdot \vec{x}^{(k)}_{6\cdot M\times 1} - \vec{b}_{N\times 1}) \neq \mathrm{pinv}(A_{N\times 6\cdot M})\cdot \vec{b}_{N\times 1}. \quad (3.18)$$

The inequality indicates that the PIGN algorithm does not guarantee to converge to the MNLSE solution of a linear problem because the product of the pseudoinverse of a rectangular matrix A and itself is not always an identity matrix. Hence, the first two terms in Eq. (3.18) do not canceled out, in general. As a result, the PIGN algorithm could only converge to a suboptimal solution to an underdetermined linear problem other than the MNLSE solution, i.e., its pseudoinverse solution plus some extra value, because the first two terms of Eq. (3.18) are not canceled out. One cannot obtain the optimal solution by using the PIGN algorithm as the learning scheme associated with the adaptive control of hyperthermia, unless there are sufficient equations.

III.F. Analysis of the result from applying the derived algorithms to BHT with temperature-dependent perfusion and thermally significant blood vessels involved

In this section, readers will learn how to utilize the IFT, optimization theory, the KKT condition, regularization, and the TPRGN algorithm to investigate the problem of nonlinear reconstruction of the system when the BHT process involves thermally significant blood vessels[45] and perfusions that depend on temperatures. Note that perfusion has been shown as an important factor affecting treatment outcomes of

TABLE I. Results when the initial guess was (1.0, 1.0, 1.0) and full reconstruction was conducted using three equations.

	Solution	2-norm of the solution	2-norm of the error of the solution	No. of iteration
True solution	(0.6299, 0.3705, 0.5751)	0.929 95	–	–
GN	(0.6210, 0.3675, 0.5903)	0.932 245	0.017 811 1	28
LM	(0.6299, 0.3705, 0.5751)	0.929 95	$1.791\,74\times 10^{-7}$	4
PIGN	(0.6299, 0.3705, 0.5751)	0.929 95	$6.949\,81\times 10^{-8}$	4

hyperthermia[46–48,24] and, in practice, it can be affected by temperature[46,49,50] and thus makes the BHT process nonlinear.

III.F.1. Issues related to the problem formulation

The first and the most important step is to formulate the output temperature as a function of the input variables, e.g., the $6^{*}M$ variables representing the ensemble of the E fields from the M sources, plus a number of $M_{\text{additional}}$ any other variables, such as those parameters related to perfusion values in different tissues. To make the formulation more explicit, the Pennes BHTs with empirically curve-fitted perfusion relations is employed to approximate temperature response to nonlinear temperature-dependent perfusion. In addition, the convective heat transfer term is also included. The convective heat transfer from thermally significant blood vessels is known to have strong influence on hyperthermia,[45,51,52]

$$\rho \cdot C_t \cdot \left(\frac{\partial T}{\partial t} + \vec{u} \cdot \nabla T \right) = \text{div}(k \text{ grad}(T)) - w_b(T) \cdot C_b \cdot (T - T_b) + Q. \quad (3.19)$$

The vector u denotes the flow velocity vector inside the thermally significant vessel. The nonlinear curves expressed below were used to simulate this phenomenon,[48,13,9,12]

$$w_{\text{tissue}} = \begin{cases} w_{\text{tissue},1} + w_{\text{tissue},2} \exp\left(\dfrac{-(T - T_{\text{crit,tissue}})^2}{s_{\text{tissue}}} \right), & T \le T_{\text{crit,tissue}} \\ w_{\text{tissue},1} + w_{\text{tissue},2}, \quad T > T_{\text{crit,tissue}} \end{cases}. \quad (3.20)$$

Then, the nonlinear system is formulated in a form of implicit function below,

$$T = T(t, \vec{r}; E_{3\times M}, \vec{u}, w_{\text{tissue},1} \cdot C_b, w_{\text{tissue},2} \cdot C_b, T_{\text{crit,tissue}}, s_{\text{tissue}}, \rho \cdot C_t, k). \quad (3.21)$$

The remaining steps for formulating the optimization problem for the nonlinear reconstruction of the system, for deriving the iterative search algorithm, and for analyzing the algorithm follow the same steps and patterns of Secs. III A–III E. In other words, all the conclusions drawn from Secs. III A–III E remain valid for very general practical hyperthermia with thermally significant vessels and temperature-dependent perfusion.

III.F.2. Issues related to the calculation or estimation of the derivatives

As shown in Eq. (2.9), the optimal solution to system reconstruction problem using nonlinear formulation is determined based on the KKT condition, and thus one needs to determine the derivatives of temperatures to unknowns. Hence, it becomes essential for one to be able to determine exactly or approximately the derivatives of the temperatures to the unknown variables.

However, in general, an explicit expression relating the unknown variables [e.g., those listed in the parentheses of Eq. (3.21)] and the temperatures is unavailable. The derivatives of the temperatures to the unknown variables are also not available. Two existing approaches were introduced below to address the determination or estimation of the derivatives of temperatures to unknowns.

A remedy for the above mentioned situation is to solve the following coupled partial differential equations (PDEs) for the temperatures and the derivatives of the temperatures from the unknown variables,

$$\rho \cdot C_t \cdot \left(\frac{\partial T}{\partial t} + \vec{u} \cdot \nabla T \right) = \text{div}(k \text{ grad}(T)) - D_b \cdot (T - T_b) + Q,$$

$$D_b \equiv w_b \cdot C_b, \quad (3.22)$$

$$\rho \cdot C_t \cdot \left(\frac{\partial \phi}{\partial t} + \vec{u} \cdot \nabla \phi \right) = \text{div}(k \text{ grad}(\phi)) - (T - T_b) - D_b \cdot \phi,$$

$$\phi \equiv \frac{\partial T}{\partial D_b}. \quad (3.23)$$

Equation (3.23) is the original PDE governing the BHT physics. The new equation [(3.23)] shows up for the purpose of determining the unknown gradient required by the iterative algorithm such as GN or LM. Notice that even in this very simplified situation in which perfusion is a single constant, the approach requires one to solve the above system of PDEs to determine the simulated temperatures and the associated derivatives. Furthermore, one should be aware that Eq. (3.23) is not linear. It is even more complicated, in practice, since perfusions are different in different tissues and follow different nonlinear dependences with temperatures [e.g., Eq. (3.20)]. Plus, this computation for the set of coupled (nonlinear) PDEs is required for every single iterative step of the learning search for system reconstruction.

TABLE II. Results when the initial guess was (1.0, 1.0, 1.0) and partial reconstruction was conducted using only the first two equations.

	Solution	2-norm of the solution	2-norm of the error of the solution	No. of iteration
True solution	(0.6299, 0.3705, 0.5751)	0.929 95	–	–
LM	(0.6160, 0.3414, 0.6406)	0.952 003	0.072 961 7	4
PIGN	(0.6160, 0.3414, 0.6406)	0.952 002	0.072 961 2	4

For example, suppose a variant of the GN algorithm is retained to reconstruct the nonlinear system with a number of 6^*M unknowns, then at least $(1+6^*M)$ of coupled (nonlinear) PDEs need to be solved at one iterative update for a single step of reconstruction. Assuming, in average, a single step of system reconstruction requires p steps to converge, then at the kth step of the reconstruction, one must conduct the computations of PDE $p^*k^*(1+6^*M)$ times in real time. Hence, this approach is not attractive for designing a real-time adaptive control of hyperthermia.

There is another approach that is better known probably because it is simpler to apply. This alternative uses a numerical approximation to estimate the derivatives of temperature to unknowns. Depending on the number of the temperatures corresponding to the perturbed unknown used to estimate the derivative, one needs to determine the same number of additional temperatures. Since one still needs to solve a PDE like Eq. (3.22) or Eq. (3.19) plus Eq. (3.20) to determine the temperature for a particular value of an unknown, there should be additional computations for PDEs to numerically estimate the derivatives. Assuming that in average a single step of system reconstruction requires p steps to converge, and that each estimation of the derivative requires q additional temperatures, then at the kth step of the reconstruction, one must conduct the computations of PDE p^*k^* $(1+q^*6^*M)$ times in a practical time frame. Therefore, this approach is also very computationally intensive.

A straightforward solution addressing the aforementioned extensive computations in real time is probably the use of parallel computation and more powerful computational hardware. Or one can try to develop an approximate temperature model that can be evaluated very fast at the same time preserving appropriate physics of hyperthermia.

III.G. A numerical example based on a set of real-valued second order equations

Another example of the problem in nonlinear system reconstruction is given to show some essential characteristics of the GN and LM algorithm. The following rules were adapted in this study for the numerical simulations using the LM algorithm. At each iterative step, the regularization parameter was chosen as 1.0×10^{-4}, and then it was halved (for the next iteration) if the value of the objective function decreases, otherwise the regularization parameter was multiplied by 2.5. In addition, the PIGN algorithm was also tested.

Equation (2.5) describes the simplified BHT process, and the major work of system reconstruction is to inversely reconstruct the components of a complex-valued second order problem. To make it simple, a real-valued model problem was used to examine some basic performances of the three algorithms,

$$\begin{cases} 0.5716 = 0.4983\cdot x_1^2 + 0.3200\cdot x_1\cdot x_2 + 0.4120\cdot x_1\cdot x_3 + 0.4399\cdot x_2^2 + 0.2126\cdot x_2\cdot x_3 + 0.1338\cdot x_3^2 \\ 0.9541 = 0.2140\cdot x_1^2 + 0.9601\cdot x_1\cdot x_2 + 0.7446\cdot x_1\cdot x_3 + 0.9334\cdot x_2^2 + 0.8392\cdot x_2\cdot x_3 + 0.2071\cdot x_3^2 \\ 0.9506 = 0.6435\cdot x_1^2 + 0.7266\cdot x_1\cdot x_2 + 0.2679\cdot x_1\cdot x_3 + 0.6833\cdot x_2^2 + 0.6288\cdot x_2\cdot x_3 + 0.6072\cdot x_3^2. \end{cases} \tag{3.24}$$

The initial guess of (x_1,x_2,x_3) was used in the first iteration, and then the chosen algorithm was used to iteratively determine the optimal solution that minimizes the square of the sum for the difference among the three equations.

The following table summarized the influences of the initial guess and the number of equations provided to the three iterative algorithms.

Based on the numerical results summarized in the previous four tables (Tables I–IV), the following facts were discovered. (1) Even when sufficient equations were provided, a bad initial guess still leads to an incorrect solution for all three tested gradient-based algorithms. (2) With insufficient equations, the performances of the LM and the PIGN algorithms are quite similar, but none of the algorithms converges

TABLE III. Results when the initial guess was (−0.2000, 1.2000, 1.0000) and full reconstruction was conducted using three equations.

	Solution	2-norm of the solution	2-norm of the error of the solution	Number of iteration
True solution	(0.6299, 0.3705, 0.5751)	0.929 95	–	–
GN	(−0.3872, 1.2129, −0.0001)	1.273 19	1.440 52	6
LM	(−0.6327, 1.1353, 0.5883)	1.426 66	1.476 24	5
PIGN	(−0.6324, 1.1355, 0.5873)	1.426 23	1.476 04	5

to the true solution when insufficient equations were supplied. These facts agree with the results of the theoretical analysis conducted in the previous Secs. III A–III E.

III.H. Numerical example based on a simplified physical model

In this section, numerical illustrations are provided to show readers another intrinsic difficulty involved in inversely reconstruct the original E fields based on the excited temperatures.

The model equation used Eq. (2.5) assumes zero initial temperature,

$$T(t,\vec{r}) = \frac{\sigma}{2 \cdot \beta \cdot \rho \cdot C_t} \cdot \vec{u}^H \cdot (E^H_{M\times 3} \cdot E_{3\times M}) \cdot \vec{u} \cdot (1 - \exp(-\beta \cdot t)) \quad (3.25)$$

The following is an ensemble of the E fields produced from the configurations given in Sec. II E:

$$E = \begin{bmatrix} -0.6540 - i \cdot 18.4009 & -50.9763 - i \cdot 68.5070 & -35.0646 - i \cdot 32.6336 \\ -61.7110 - i \cdot 10.9476 & -55.9187 - i \cdot 44.1251 & -83.3993 - i \cdot 67.5388 \\ -36.1327 - i \cdot 79.3490 & -20.0352 - i \cdot 49.0499 & -17.5995 - i \cdot 12.4801 \end{bmatrix}. \quad (3.26)$$

However, the temperature excited by the above ensemble of the E fields is very close to that by the very different ensemble of the E fields below,

$$E = \begin{bmatrix} 54.8752 + i \cdot 23.6583 & 68.3855 + i \cdot 45.3003 & 58.7610 + i \cdot 47.8418 \\ 35.5216 + i \cdot 40.7102 & 34.0176 + i \cdot 58.6614 & 42.5001 + i \cdot 50.3939 \\ 29.5917 + i \cdot 32.7615 & 31.8210 + i \cdot 47.0263 & 28.9420 + i \cdot 38.4557 \end{bmatrix}. \quad (3.27)$$

Suppose that a driving vector given below was used to excite the above two ensembles of E fields, the corresponding temperatures were 1.1463 [when Eq. (3.26) is plugged into Eq. (3.25)] and 1.1065 [when Eq. (3.27) is plugged into Eq. (3.25)],

$$\vec{u} = \begin{Bmatrix} 0.0430 + i \cdot 0.9251 \\ 0.7469 + i \cdot 0.0270 \\ 0.7505 + i \cdot 0.6824 \end{Bmatrix}. \quad (3.28)$$

This result indicates that there are two very different ensembles of E fields producing temperatures that are very close. Since measurement error is unavoidable, this result implies that the system reconstructed might be very different from the true one. Hence, using a temperature measuring technique having high accuracy would be very advantageous when using a nonlinear system reconstruction. Meanwhile, the sensitivity shown in this result also implies the importance of imposing a constraint on the norm of the solution to be reconstructed. This sensitivity provides another important reason to use the regularization approach.

III.I. Comparison between linear and nonlinear formulations of system reconstruction

System reconstruction using nonlinear formulation is theoretically more advantageous than linear formulation for it demands fewer learning correction steps, provided the number of heat sources is greater than 6. However, in practice, this theoretical advantage is diminished by the significant computational loads of evaluating or estimating the derivatives of temperature to unknowns, as analyzed in Sec. III F 2.

Assuming one can develop an efficient way to evaluate or estimate these derivatives such as using a simplified BHTE model [e.g., Eq. (2.5)] or a parallel algorithm; one still needs to perform at least 36 learning steps of system reconstruction, assuming there are only six independent sources. According to the analyses shown in Secs. III C and III D, one

TABLE IV. Results when the initial guess was (−0.2000, 1.2000, 1.0000) and partial reconstruction was conducted using only the first two equations.

	Solution	2-norm of the solution	2-norm of the error of the solution	No. of iteration
True solution	(0.6299, 0.3705, 0.5751)	0.929 95	–	–
LM	(−0.6327, 1.1353, 0.5883)	1.426 66	1.476 24	5
PIGN	(−0.6324, 1.1355, 0.5873)	1.426 23	1.476 04	5

does not have a solid theoretical support to optimally reconstruct the true system before these steps. Adding regularization is mandatory to formulate a well-posed problem of partial reconstruction, and it increases the chance to optimally reconstruct the system within 36 steps, but again, there is no theoretical guarantee of this success. Besides, the nonlinear reconstruction that identifies the ensemble of E fields using temperature feedbacks is sensitive to the perturbations involved, as shown in Sec. III H, and thus, a sufficient time period becomes necessary for imaging facility to retrieve accurate temperature image feedback during each correction session. When MRI is used, the length of this time interval of 5 min was suggested.[53,15] Hence, in principle, a total time of 180 min ($180=5^*36$) would be required for the optimal system reconstruction using nonlinear approach; this is not clinically appealing.

This undesirably long time of nonlinear reconstruction can be shortened if a model reduction method is developed to reduce the number of unknown variables,[12] and apparently, the fewer the better. However, a nonlinear formulation is not theoretically better than a linear formulation, if the number of sources is less than 6. That is, incorporating a method of model reduction reduces the learning time of nonlinear formulation, but, when the number of independent variables is less than 6, an even shorter learning time results if one uses a linear formulation having the same number of unknowns reduced from a method of model reduction. In addition, the nonlinear reconstruction formulated in Eq. (2.4) does not identify any thermal properties such as thermal diffusivity or blood perfusion. Consequently, one must design and implement another algorithm to identify these unknowns, e.g., Eq. (3.21), which, in turn, demanding extra time and effort. However, without this information, one cannot determine the optimal driving vector that optimally elevates the temperature distribution. In contrast, the linear formulation already taking these thermally related factors into account in an implicit form,[8] and thus, once identified, the optimal driving vector determined directly satisfies an objective function optimizing temperature.[8,11,12] Taking all these considerations into account, a more clinically attractive option appears to be the combination of a linear formulation and a model reduction.[11,12]

IV. CONCLUSIONS AND SUGGESTIONS TO FUTURE DIRECTION

Problem formulation has strong influence on the efficiency and accuracy of system reconstruction in hyperthermia therapy. Formulating in nonlinear form results in a theoretically fewer correction steps than formulating in linear form for the system reconstruction embedded in the adaptive control of hyperthermia, provided the number of independent heat sources is greater than 6. Besides, formulating a regularized optimization problem is mandatory when attempting using partial reconstruction to shorten the time required for the learning improvements of the mathematical description of the system to the integrated environment of patient and the heating facility. Otherwise, one does not have a solid theoretical support to optimally reconstruct the optimal system, regardless of which algorithm to use for the problem of nonlinear partial reconstruction. In a word, one must formulate the problem at hand properly before designing or employing an algorithm to solve a problem.

When a full reconstruction method (NNLFR or NNYFR) is used, the LM algorithm is suggested for solving the problem of system reconstruction. Nevertheless, in the presence of noise, the TPRGN algorithm might have better performance in reconstructing an approximate system, especially when one has reliable *a priori* information in physics to supplement a good guessed system. On the other hand, when a partial reconstruction (NNLPR or NNYPR) is employed, both the LM and the GN algorithms cannot be used. Instead, one must first regularize the original reconstruction problem to make it well posed. Then, the TPRGN algorithm is recommended. The TPRGN algorithm can incorporate *a priori* information and thus increase the chance to reconstruct an optimal system before its theoretical iterations required by IFT. Moreover, the users of the TPRGN algorithm can design an appropriate regularization term to reduce the negative influences from the unavoidable measurement noise. Nonetheless, an estimate, in advance, on the steps required by an iterative searching algorithm to solve a nonlinear partial reconstruction problem remains unavailable. In addition, to ensure its convergence to the true solution, a good initial guess very close to the true solution must be supplemented with the LM or TPRGN algorithm.

Finally, the extensive computational works required to evaluate or estimate the derivatives of temperature with respect to the variables to be identified severely diminishes the attractiveness of using nonlinear formulation. This motivates the development of model reduction[12] so that these derivatives can be determined or estimated in a practical clinical time frame. An alternative is the development of fast numerical solver to the Penne BHTE to accelerate the computation of the derivatives, e.g., implementing a parallel algorithm for the BHTE.

ACKNOWLEDGMENTS

The authors thank Professor Robert Israel of the Department of Mathematics at the University of British Columbia, Canada, and Professor Elena Cherkaev of the Department of Mathematics at the University of Utah, USA for suggestions. The authors thank the comments and suggestions made by the two reviewers, especially the suggestion made by the first reviewer, in which the author was reminded to provide more detailed explanations on the workloads required by linear and nonlinear learning algorithms. The authors also thank Elisa H. Jenny, MSc, for the help on collecting literatures. This study was supported by NIH grant NCI P01—CA042745-23.

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[1]E. Jones, D. Thrall, M. W. Dewhirst, and Z. Vujaskovic, "Prospective thermal dosimetry: The key to hyperthermia's future," Int. J. Hyperthermia **22**, 247–253 (2006).

[2]R. D. Issels, "High-risk soft tissue sarcoma: Clinical trial and hyperthermia combined chemotherapy," Int. J. Hyperthermia **22**, 235–239 (2006).

[3]J. Gellermann, B. Hildebrandt, R. Issels, H. Ganter, W. Wlodarczyk, V. Budach, R. Felix, P. U. Tunn, P. Reichardt, and P. Wust, "Noninvasive magnetic resonance thermography of soft tissue sarcomas during regional hyperthermia—Correlation with response and direct thermometry," Cancer **107**, 1373–1382 (2006).

[4]J. Gellermann, M. Weihrauch, C. H. Cho, W. Wlodarczyk, H. Fahling, R. Felix, V. Budach, M. Weiser, J. Nadobny, and P. Wust, "Comparison of MR-thermography and planning calculations in phantoms," Med. Phys. **33**, 3912–3920 (2006).

[5]P. Wust, C. H. Cho, B. Hildebrandt, and J. Gellermann, "Thermal monitoring: Invasive, minimal-invasive and non-invasive approaches," Int. J. Hyperthermia **22**, 255–262 (2006).

[6]S. A. Goss, R. L. Johnston, and F. Dunn, "Comprehensive compilation of empirical ultrasonic properties of mammalian tissues," J. Acoust. Soc. Am. **64**, 423–457 (1978).

[7]S. Gabriel, R. W. Lau, and C. Gabriel, "The dielectric properties of biological tissues. III. Parametric models for the dielectric spectrum of tissues," Phys. Med. Biol. **41**, 2271–2293 (1996).

[8]K.-S. Cheng, V. Stakhursky, P. R. Stauffer, M. W. Dewhirst, and S. K. Das, "Online feedback focusing algorithm for hyperthermia cancer treatment," Int. J. Hyperthermia **23**, 539–554 (2007).

[9]K.-S. Cheng, V. Stakhursky, O. I. Craciunescu, P. Stauffer, M. Dewhirst, and S. K. Das, "Fast temperature optimization of multi-source hyperthermia applicators with reduced-order modeling of 'virtual sources'," Phys. Med. Biol. **53**, 1619–1635 (2008).

[10]M. Seebass, R. Beck, J. Gellermann, J. Nadobny, and P. Wust, "Electromagnetic phased arrays for regional hyperthermia: Optimal frequency and antenna arrangement," Int. J. Hyperthermia **17**, 321–336 (2001).

[11]K.-S. Cheng, Y. Yuan, Z. Li, P. R. Stauffer, W. T. Joines, M. W. Dewhirst, and S. K. Das, "Control time reduction using virtual source projection for treating a leg sarcoma with nonlinear perfusion," SPIE Photonics West, San Jose, CA, 24–29 January 2009, Vol. 7181 (unpublished).

[12]K.-S. Cheng, Y. Yuan, Z. Li, P. R. Stauffer, P. Maccarini, W. T. Joines, M. W. Dewhirst, and S. K. Das, "Performance of a reduced-order adaptive controller when used in multi-antenna hyperthermia treatments with nonlinear temperature-dependent perfusion," Phys. Med. Biol. **54**, 1979–1995 (2009).

[13]M. E. Kowalski and J.-M. Jin, "A temperature-based feedback control system for electromagnetic phased-array hyperthermia: Theory and simulation," Phys. Med. Biol. **48**, 633–651 (2003).

[14]K.-S. Cheng, M.W. Dewhirst, P. R. Stauffer, and S. Das, "Effective learning strategies for real-time image-guided adaptive control of multiple source hyperthermia applicators," Med. Phys. **37** (2010).

[15]M. Weihrauch, P. Wust, M. Weiser, J. Nadobny, S. Eisenhardt, V. Budach, and J. Gellermann, "Adaptation of antenna profiles for control of MR guided hyperthermia (HT) in a hybrid MR-HT system," Med. Phys. **34**, 4717–4725 (2007).

[16]G. Dorfleitner, P. Schneider, K. Hawlitschek, and A. Buch, "Pricing options with Green's functions when volatility, interest rate and barriers depend on time," Quant. Finance **8**, 119–133 (2008).

[17]P. Fotiu, "Integral equation analysis of elastic-viscoplastic fracturing plates under dynamic loading," *Proceedings of the Second International Conference on Computational Plasticity, Models, Software and Applications* (Pineridge, Swansea, 1989), pp. 1171–1182.

[18]A. El-Azab and N. M. Ghoniem, "Green's function for the elastic field of an edge dislocation in a finite orthotropic medium," Int. J. Fract. **61**, 17–37 (1993).

[19]C. Toepffer and C. Cercignani, "Analytical results for the Boltzmann equation," Contrib. Plasma Phys. **37**, 279–291 (1997).

[20]C. A. Balanis, *Advanced Engineering Electromagnetics* (Wiley, New York, 1989), Solution Manual ed.

[21]H. H. Pennes, "Analysis of tissue and arterial blood temperatures in the resting human forearm," J. Appl. Physiol. **1**, 93–122 (1948).

[22]K.-S. Cheng and R. B. Roemer, "Closed-form solution for the thermal dose delivered during single pulse thermal therapies," Int. J. Hyperthermia **21**, 215–230 (2005).

[23]R. B. Roemer, "The local tissue cooling coefficient: A unified approach to thermal washout and steady-state 'perfusion' calculation," Int. J. Hyperthermia **6**, 421–430 (1990).

[24]K.-S. Cheng and R. B. Roemer, "Blood perfusion and thermal conduction effects in Gaussian beam, minimum time single-pulse thermal therapies," Med. Phys. **32**, 311–317 (2005).

[25]L. Cesari, "The implicit function theorem in functional analysis," Duke Math. J. **33**, 417–440 (1966).

[26]T. H. McNicholl, "Computability and the implicit function theorem," Electron. Notes Theor. Comput. Sci. **167**, 3–15 (2007).

[27]H. W. Kuhn and A. W. Tucker, presented at the Proceedings of the Second Berkeley Symposium, Berkeley, CA, 1951, pp. 481–492 (unpublished).

[28]C. Gabriel, S. Gabriel, and E. Corthout, "The dielectric properties of biological tissues. I. Literature survey," Phys. Med. Biol. **41**, 2231–2249 (1996).

[29]S. Gabriel, R. W. Lau, and C. Gabriel, "The dielectric properties of biological tissues. II. Measurements in the frequency range 10 Hz to 20 GHz," Phys. Med. Biol. **41**, 2251–2269 (1996).

[30]W. H. Hayt, Jr. and J. A. Buck, *Engineering Electromagnetics*, 7th ed. (McGraw-Hill Higher Education, New York, 2006).

[31]C. A. T. Van den Berg, J. B. Van De Kamer, A. A. C. De Leeuw, C. R. L. P. N. Jeukens, B. W. Raaymakers, M. Van Vulpen, and J. J. W. Lagendijk, "Towards patient specific thermal modelling of the prostate," Phys. Med. Biol. **51**, 809–825 (2006).

[32]C. F. Gauss, *Theory of the motion of the heavenly bodies moving about the sun in conic sections* (Dover, New York, 1963).

[33]P. Deuflhard and V. Apostolescu, Amsterdam, Netherlands, 1980 (unpublished).

[34]K. Levenberg, "A method for the solution of certain non-linear problems in least squares," Q. Appl. Math. **2**, 164–168 (1944).

[35]D. Marquardt, "An algorithm for least-squares estimation of nonlinear parameters," SIAM J. Appl. Math. **11**, 431–441 (1963).

[36]P. Wust, H. Fahling, W. Wlodarczyk, M. Seebass, J. Gellermann, P. Deuflhard, and J. Nadobny, "Antenna arrays in the SIGMA-eye applicator: Interactions and transforming networks," Med. Phys. **28**, 1793–1805 (2001).

[37]J. Hadamard, "Sur les problemes aux derivees partielles et leur signification physique," Princeton University Bulletin **13**, 49–52 (1902).

[38]D. L. Philips, "A technique for numerical solution of certain integral equations of the first kind," J. Assoc. Comput. Mach. **9**, 84–97 (1962).

[39]A.-I. N. Tikhonov, "Regularization of incorrectly posed problems," Sov. Math. Dokl. **4**, 1624–1627 (1963).

[40]C. M. Leung and W.-S. Lu, presented at the Proceedings of the Canadian Conference on Electrical and Computer Engineering, Vancouver, BC, Canada, 14–17 September 1993 (unpublished).

[41]U. Amato and W. Hughes, "Maximum entropy regularization of Fredholm integral equations of the first kind," Inverse Probl. **7**, 793–808 (1991).

[42]T. Schröter and U. Tautenhahn, "Error estimates for Tikhonov regulariza-

tion in Hilbert scales," Numer. Funct. Anal. Optim. **15**, 155–168 (1994).
[43]E. H. Moore, "On the reciprocal of the general algebraic matrix," Bull. Am. Math. Soc. **26**, 394–395 (1920).
[44]R. Penrose, presented at the Proceedings of the Cambridge Philosophical Society, 1955 (unpublished).
[45]J. W. Baish, P. S. Ayyaswamy, and K. R. Foster, "Heat transport mechanisms in vascular tissues: A model comparison," J. Biomech. Eng. **108**, 324–331 (1986).
[46]C. W. Song, A. Lokshina, J. G. Rhee, M. Patten, and S. H. Levitt, "Implication of blood flow in hyperthermia treatment of tumors," IEEE Trans. Biomed. Eng. **BME-31**, 9–16 (1984).
[47]D. T. Tompkinsn, R. Vanderby, S. A. Klein, W. A. Beckman, D. M. Steeves, D. M. Frey, and B. R. Palival, "Temperature-dependent versus constant rate blood perfusion modeling in ferromagnetic thermoseed hyperthermia," Int. J. Hyperthermia **10**, 517–536 (1994).
[48]J. Lang, B. Erdmann, and M. Seebass, "Impact of nonlinear heat transfer on temperature control in regional hyperthermia," IEEE Trans. Biomed. Eng. **46**, 1129–1138 (1999).
[49]R. B. Roemer, J. R. Oleson, and T. C. Cetas, "Oscillatory vasoactivity response to constant power," Am. J. Physiol. **249**, R153–R158 (1985).
[50]D. Akyürekli, L. H. Gerig, and G. P. Raaphorst, "Changes in muscle blood flow distribution during hyperthermia," Int. J. Hyperthermia **13**, 481–496 (1997).
[51]J. Song, L. X. Xu, D. E. Lemons, and S. Weinbaum, "Enhancement in the effective thermal conductivity in rat spinotrapezius due to vasoregulation," J.Biomech. Eng. **119**, 461–468 (1997).
[52]D. Shrivastava and R. B. Roemer, "Readdressing the issue of thermally significant blood vessels using a countercurrent vessel network," J. Biomech. Eng. **128**, 210–216 (2006).
[53]J. Nadobny, W. Wlodarczyk, L. Westhoff, J. Gellermann, R. Felix, and P. Wust, "A clinical water-coated antenna applicator for MR-controlled deep-body hyperthermia: A comparison of calculated and measured 3-D temperature data sets," IEEE Trans. Biomed. Eng. **52**, 505–519 (2005).