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Fast temperature optimization of multi-source hyperthermia applicators with reduced-order modeling of ‘virtual sources’

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Abstract

The goal of this work is to build the foundation for facilitating real-time magnetic resonance image guided patient treatment for heating systems with a large number of physical sources (e.g. antennas). Achieving this goal requires knowledge of how the temperature distribution will be affected by changing each source individually, which requires time expenditure on the order of the square of the number of sources. To reduce computation time, we propose a model reduction approach that combines a smaller number of predefined source configurations (fewer than the number of actual sources) that are most likely to heat tumor. The source configurations consist of magnitude and phase source excitation values for each actual source and may be computed from a CT scan based plan or a simplified generic model of the corresponding patient anatomy. Each pre-calculated source configuration is considered a ‘virtual source’. We assume that the actual best source settings can be represented effectively as weighted combinations of the virtual sources. In the context of optimization, each source configuration is treated equivalently to one physical source. This model reduction approach is tested on a patient upper-leg tumor model (with and without temperature-dependent perfusion), heated using a 140 MHz ten-antenna cylindrical mini-annular phased array. Numerical simulations demonstrate that using only a few pre-defined source configurations can achieve temperature distributions that are comparable to those from full optimizations using all physical sources. The method yields close to optimal temperature distributions when using source configurations determined from a simplified model of the tumor, even when tumor position is erroneously assumed to be ~2.0 cm away from the actual position as often happens in practical clinical application of pre-treatment planning. The method also appears to be robust under conditions of changing, nonlinear, temperature-dependent perfusion. The proposed approach of using virtual sources reduces the number of variables that must be optimized to achieve a tumor-focused temperature distribution, thereby reducing the calculation time required in real-time control applications to about 1/3 to 1/4 of that required for full optimization.

1. Introduction

Hyperthermia that maintains a higher than normal temperature in tumor has been found to enhance the efficacy of radiotherapy and chemotherapy (Ahn *et al.* 2003, Madsen *et al.* 2005, Dewhirst *et al.* 2006). Selectively focusing heat in the tumor is complicated by the various interactions of electromagnetic/ultrasound waves in intervening tissue. Magnetic resonance image (MRI) based temperature measurement is increasingly being utilized to monitor hyperthermia treatments in real-time (Hynynen *et al.* 1995, Salomir *et al.* 2000, Salomir 2001, Hynynen and McDannold 2004, Wust *et al.* 2006, Gellermann *et al.* 2006).

Real-time MRI-based temperature measurement may also be extended to treatment optimization, to effectively steer heating to the tumor. Prior work has laid the foundation for this development (Das *et al.* 1999). However, the overhead time with the patient inside the magnet bore required to create an MRI-based mathematical model, relating applied source

configurations to resulting temperature distributions, is proportional to the square of the number of heating sources (Das *et al* 1999). Thus, this technique could be prohibitively time intensive for heating systems with a large number of physical (e.g. antenna) sources. The goal of this work is to lay the foundation for facilitating real-time control of patient treatments with large multi-antenna heating systems, by effectively reducing the number of independent heat sources in the calculations and corresponding optimization times.

The approach adopted here is based on the idea that it is possible, prior to patient treatment, to identify and rank several linearly independent predefined source-setting configurations that are most likely to be candidates for effective tumor heating. Each configuration is composed of a set of magnitudes and phases for all physical sources. This pre-calculated source configuration is considered as a 'virtual source', which effectively functions as if it were one heat source. Thus, turning on a predefined source configuration or a 'virtual source' is equivalent to turning on all physical sources with specific magnitudes and phases. This *a priori* determination is based on a model of the patient and tumor, and the assumption that the optimal source configuration that most efficiently heats the tumor can be identified at treatment time by searching only within a reduced subspace defined by a previously determined smaller subset of possible source configurations. In essence, we propose that for $N < M$ (M = number of physical sources) representative linearly independent virtual sources, the overhead time involved in creating an MRI-based model can be reduced substantially, since $N^2 \ll M^2$. The focus of this work is validation of the virtual source approach by addressing two following issues.

- a. Can a smaller number of linearly independent virtual sources provide a sufficiently good optimization solution, i.e., a solution that is almost as good as a full optimization with all physical sources?
- b. Is the virtual source approach sufficiently robust to simplified models of the patient geometry to yield optimization results comparable to results using anatomically complete geometry and all physical sources?

These two questions are addressed via numerical simulations of a patient upper-leg tumor model heated with a ten-antenna mini-annular-phased-array electromagnetic applicator.

2. Methods and materials

2.1. Derivation of a parametric model combining power and temperature

The physical models involved in a hyperthermia treatment are the power model, which computes the EM or ultrasound (US) power distribution in the heated domain, and the bio-heat transfer model, which takes the power distribution as input to compute the temperature distribution. The current work assumes an EM-heating system. The EM field at any spatial location can be written as

$$\vec{E}_{\text{sum}} = \sum_{m=1}^M u_m \cdot \vec{E}_m = [\vec{E}_1 \cdots \vec{E}_M] \cdot \begin{pmatrix} u_1 \\ \vdots \\ u_M \end{pmatrix} \quad (1)$$

where M is the number of antennas, E_m is the electric field from antenna m , and u_m is the complex source input value for antenna m . The above equation states that the resultant electric field is the weighted sum of the individual electric fields generated by each of the EM wave sources. The tissue-absorbed power distribution of this resultant electric field can then be written in Hermitian form (Boag and Leviatan 1988):

$$\begin{aligned}
 P_{\text{sum}} &= \frac{\sigma}{2} \cdot \vec{E}_{\text{sum}} \bullet \vec{E}_{\text{sum}} = \frac{\sigma}{2} \cdot [u_1^H \cdots u_M^H] \cdot \begin{Bmatrix} \vec{E}_1^H \\ \vdots \\ \vec{E}_M^H \end{Bmatrix} \bullet [\vec{E}_1 \cdots \vec{E}_M] \cdot \begin{Bmatrix} u_1 \\ \vdots \\ u_M \end{Bmatrix} \\
 &= \frac{\sigma}{2} \cdot [u_1^H \cdots u_M^H] \cdot [\Phi_{i,j}] \cdot \begin{Bmatrix} u_1 \\ \vdots \\ u_M \end{Bmatrix}, \quad i=1, \dots, M, \quad j=1, \dots, M,
 \end{aligned} \tag{2}$$

where superscript H denotes complex-conjugate transpose. Next, without knowing the exact form of the bio-heat transfer equation, the temperature distribution with zero boundary conditions can be expressed in terms of Green's function (the impulse response function, a result of applying both the superposition property and the homogeneity property) as follows (Rugh 1996):

$$\begin{aligned}
 T(x_i, y_j, z_k) &= \int_{V_H} (G(x_i - x', y_j - y', z_k - z') \cdot P_{\text{sum}}(x', y', z')) \cdot dx' \cdot dy' \cdot dz' \\
 &= \vec{u}^H \cdot [S_{i,j,k}] \cdot \vec{u},
 \end{aligned} \tag{3}$$

where i, j, k denote indices of the nodes along the x, y and z direction. Note that the point-wise system matrices $[S_{i,j,k}]$ are Hermitian, and $\vec{u}$ is the driving vector. The temperature solution expressed by equation (3) is valid for any linear model such as the k -effective model (Bowman *et al* 1989), the Pennes bio-heat transfer model, given below (Pennes 1948), or a combination of both models.

$$\frac{1}{\rho \cdot C_t} \cdot \nabla \bullet (k \cdot \nabla T) - \frac{\omega_b \cdot C_b}{\rho \cdot C_t} \cdot T + \frac{Q}{\rho \cdot C_t} = 0. \tag{4}$$

The elements of the point-wise matrices $[S_{i,j,k}]$ can be computed for an M -antenna system from either M^2 linearly independent MR thermal images or M^2 linearly independent bio-heat transfer computer simulations (Das *et al* 1999, Cheng *et al* 2007a, 2007b). Following the determination of the point-wise matrices, they may be used to determine the temperature distribution for any arbitrary antenna configurations.

2.2. Derivation of a reduced-order model

Equation (3) suggests that model reduction can be achieved by assuming that the optimal-treatment driving vector ($\vec{u}$) is contained in a predefined vector subspace of smaller dimension than the number of antennas.

$$T(x_i, y_j, z_k) \approx (X \cdot \vec{c})^H \cdot [S_{i,j,k}] \cdot (X \cdot \vec{c}) \tag{5}$$

where X is the smaller subspace (dimension $M \times N$, $N < M$), and $\vec{c}$ is the $N \times 1$ vector of multipliers that combines the columns of X . Essentially, this method recognizes that the wave sources described in equation (1) need not just be individual physical antennas. Rather, the wave sources could be conceptualized as specific weighted combinations of individual physical antennas (represented by the columns of X). Each of these specific weighted combinations of physical antenna magnitude and phase excitation parameters may be thought of as a 'predefined source configuration' or a 'virtual source'. In the context of equation (5), the elements of vector

$\vec{c}$ can then be regarded as the weights for the virtual sources. The transformation from equations (3)–(5) reduces the unknowns from $\vec{u}$ (M -dimensional vector) to $\vec{c}$ (N -dimensional vector). Thus, the time overhead required to construct the model using MR thermal images can be significantly lowered by a factor of $(N/M)^2$.

In this work, we construct a reduced-order matrix (X) with predefined source configuration vectors constituting the linearly independent columns of X . The linearly independent virtual sources are computed to maximize average tumor temperature per unit magnitude input vector. To compute those linearly independent virtual sources of unit magnitude, all tumor point-wise system matrices $S_{i,j,k}$ are summed and arithmetically averaged, following which only the first few eigenvectors with largest eigenvalues of this averaged tumor matrix are chosen for the virtual sources. From the Rayleigh–Ritz theorem, e.g. (Parlett 1980), these first few eigenvectors maximize the arithmetically averaged tumor temperature most effectively:

$$\begin{aligned}
 [S_{i,j,k}]_{\text{averaged tumor}} &= \frac{1}{N_{\text{tumor}}} \cdot \sum_{m=1}^{N_{\text{tumor}}} [S_{i,j,k}]_m \\
 &= \sum_{n=1}^{N_{\text{physical source}}} \lambda_n \cdot \vec{v}_n \cdot \vec{v}_n^H, \lambda_1 \geq \dots \geq \lambda_{N_{\text{physical source}}} \\
 &\Rightarrow \text{set of virtual sources: } \{\vec{v}_n\}_{n=1}^{N_{\text{virtual source}}}, N_{\text{virtual source}} \leq N_{\text{physical source}}.
 \end{aligned} \tag{6}$$

Since those point-wise system matrices are Hermitian, their arithmetic average is also Hermitian. From spectral decomposition theory (Keener 2000), this matrix has a complete set of eigenvectors to express any possible heating vectors of the given patient geometry, tumor position and heating applicator.

At this stage, the complete set of eigenvectors, which are linearly independent virtual sources of unit magnitudes, are determined analytically based on an optimal criterion that optimizes the averaged tumor temperature. However, a practical hyperthermia treatment must deliver an optimized temperature distribution that maximizes tumor temperatures and minimizes normal tissues temperatures. Therefore, numerical optimization that attempts to maximize tumor heating while maintaining normal tissue at relatively lower temperature is given in the following section.

2.3. Formulation of an optimization problem for numerical examples

To validate the proposed problem reduction approach, numerical optimization simulations were run for EM heating of a human upper-leg dataset (see figure 1(a)). The heating device is a simulated mini-annular-phased array (MAPA) of ten equispaced paired dipole antennas mapped on the surface of a cylindrical applicator of diameter 23 cm and length 27.5 cm (see figure 1(a)). This is a design extension of the BSD-2000 SIGMA 30 system (Salt Lake City, UT), which has only four pairs of dipole antennas in a cylindrical-phased array. The patient model was centered within this heating device, with a coupling water bolus filling the space between the leg and outer cylinder. The 3D EM fields for each of the ten antennas were simulated for 140 MHz using commercial finite element (FE) based software (HFSS Ansoft Corporation (Pittsburgh, PA)). The simulated EM fields were linearly interpolated to a uniform grid of 4.0 mm and then used as the heat source for 3D temperature simulations using the successive over-relaxation (SOR) finite difference method. A constant uniform temperature of 37 °C was used as the boundary condition. The property values used are adapted from literature (Gabriel *et al* 1996a, 1996b, 1996c, Hayt and Buck 2006) and are summarized in table 1.

Permittivity of vacuum, $\epsilon_0 = 8.854 \times 10^{-12}$ farad m^{-1} and permeability of vacuum, $\mu_0 = 4 \times \pi \times 10^{-7}$ H m^{-1} . All tissues' permabilities were assumed to be equal to that of vacuum.

To apply this method to practical treatment applications, users can easily design different objective functions specific to their applications, for example, the desired tumor temperature and (safe) normal tissue temperature for adjuvant hyperthermia combined with chemotherapy or radiation (tumor at $\sim 40\text{--}44$ °C, with normal tissue temperatures below 40 °C) (Stauffer and Goldberg 2004). Therefore, an optimal treatment goal is assumed to be all tumor temperatures close to 50 °C distribution and normal tissues close to 40 °C. Because extremity sarcomas are known to contain necrotic areas that often fill with fluid, those pockets of stagnant fluid can heat up to 50 °C, as we observed in clinics. The objective function for this case is given below. A weighting factor of $w = 2$ is added to bias the optimal result toward tumor heating:

$$J = \frac{1}{N_{\text{normal}} + N_{\text{tumor}}} \cdot \left(\sum_{n=1}^{N_{\text{normal}}} (T_n - 40)^2 + w \cdot \sum_{n=1}^{N_{\text{tumor}}} (T_n - 50)^2 \right), \quad w=2. \quad (7)$$

The above criterion attempts to uniformize tumor temperature to 50 °C and normal tissues at 40 °C. This is a less sophisticated objective than one that would only penalize normal tissue above 40 °C and tumor below 50 °C. The temperature at each point in the domain is expressed as in equation (5), with unknowns, vector $\vec{c}$ optimized to minimize the objective function value. The optimal goal is deemed exactly achieved when the value of the objective function equals zero.

2.4. Robustness studies

The effects of three sources of uncertainties on the robustness of the virtual source methodology were studied: (a) noise in the M^2 MR thermal images used to generate the system matrices (equation (3)) for tumor heating at every point, (b) variable electrical and thermal properties of the tissue model, and (c) temperature-dependent perfusion.

2.4.1. MR thermal image noise—Since the eventual use for the virtual source methodology is in the context of actual temperature measurements, such as from MR thermal images, a certain amount of noise is likely to be present. Experimentally, the 3D temperature measurements could be conducted using MRI methods such as proton resonance frequency shift (PRFS) or apparent diffusion coefficient (ADC) (Gellermann *et al* 2005). As the PRFS method provides more stable measurements than the ADC method (Gellermann *et al* 2005), we used the PRFS method for our MRI measurement. Noise estimates are based on our experimental data obtained by repeatedly imaging phantoms over the typical duration of a hyperthermia treatment (~ 70 min) in the absence of any heating. The image parameters used in our experiment were $T_r = 34$ ms, $T_e = 20$ ms, 30° flip angle, number of excitations = 1, field of view of 24 cm (GE Signal 1.5 T MRI system). A proton phase angle difference between two sequential images is proportional to the rise in local temperature, and therefore phase noise will be directly converted to temperature noise. For a number of phase difference images (taken in the same z -plane location), square regions of interest (ROI) of size 50-by-50 pixels were analyzed for the variation in phase difference (see figure 2). The phase difference histograms were approximately Gaussian with a full-width-half-maximum ranging from 0.02 to 0.045 rad, depending on the location of the square window (see figure 2). This phase spread was converted to a temperature standard deviation of 0.3 °C, using an experimentally computed conversion factor (MacFall *et al* 1996). Therefore, to determine robustness of the virtual sources in the presence of noise, Gaussian white noise with zero mean and 0.3 °C standard deviation was added to the simulated temperature field.

2.4.2. Model uncertainty—The columns of X , constituting the virtual source bases in equation (5), are the eigenvectors corresponding to the first few largest eigenvalues of the tumor-averaged matrix. Since this approach requires prior knowledge of the patient and tumor geometry, it can only be computed after acquisition of the CT dataset and computation of the electric fields, a process that requires considerable time expenditure: 1–2 days if built manually (Wust *et al* 1998) and ~4 h, if built semi-automatically (Piket-May *et al* 1992, Wust *et al* 1998). A faster approach, better suited to real-time treatment, is to compute virtual source bases from a simplified ‘generic patient’ geometry. In this work, the simplified model (figure 1(b)) is a truncated elliptical cone with muscle equivalent properties. Dimensions for the truncated cone model of a leg tumor are as follows: length = 40 cm; larger cone base ellipse radii = 10.5 cm, 8.6 cm; smaller cone base ellipse radii = 8 cm, 6 cm. The tumor is assumed to be cylindrical, with dimensions: length = 10.0 cm, radius = 3.2 cm. Three tumor locations were considered: (a) tumor located as in the actual patient geometry, (b) tumor displaced 2.0 cm along the y direction, (c) tumor location displaced 2.0 cm along each of the x and y directions. In essence, these tumor locations sequentially increase the degree of model error.

The virtual source bases obtained from this simplified geometry, figure 1(b) (approximate virtual source bases: X^* in place of X in equation (5)) were evaluated for their effectiveness in tumor heating. A measure of optimization deterioration was used to judge the effectiveness of the approximate virtual source bases: $(J^* - J)$, where J^* is the optimized objective value obtained with X^* , and J is the optimized objective value from all physical antennas, (see equation (7)).

2.4.3. Temperature-dependent perfusion—This work also studies robustness of the virtual source approach to temperature-dependent perfusion. It is known that blood perfusion plays an important role in hyperthermia (Song *et al* 1984, Tompkins *et al* 1994, Lang *et al* 1999, Cheng and Roemer 2005) and that the perfusion changes as a function of temperature elevation (Song *et al* 1984, Sekins *et al* 1984, Roemer *et al* 1985, Akyurekli *et al* 1997). A set of temperature-dependent perfusion equations were assumed here. The equations for fat and muscle were modeled as logistic functions relating temperature to perfusion, thereby attempting to mimic the trend observed in experimental data (Song *et al* 1984). In developing these functions, we assumed that perfusion increases with temperature in all tissue, ranging from 30% below to 30% above the constant perfusion values in table 1 (see figure 3):

$$w_{\text{fat}} = \begin{cases} 0.77 + 0.66 \cdot \exp\left(\frac{-(T-45.0)^2}{12.0}\right), & T \leq 45.0 \\ 1.43, & T > 45.0 \end{cases} \quad (8a)$$

$$w_{\text{muscle}} = \begin{cases} 2.52 + 2.16 \cdot \exp\left(\frac{-(T-45.0)^2}{12.0}\right), & T \leq 45.0 \\ 4.68, & T > 45.0 \end{cases} \quad (8b)$$

$$w_{\text{tumor}} = \begin{cases} 1.26 + 1.08 \cdot \exp\left(\frac{-(T-45.0)^2}{12.0}\right), & T \leq 45.0 \\ 2.34, & T > 45.0. \end{cases} \quad (8c)$$

Here w denotes blood perfusion in fat, muscle or tumor. Blood perfusion dynamics remains an open research topic and therefore the above perfusion-temperature equations must be considered speculative. Optimization simulations were performed in the realistic patient CT

thigh model (figure 1(a)) and the simplified thigh model (figure 1(b)). The elements of the point-wise matrices (S , see equation (5)) were determined from a set of M^2 test ‘images’, generated using the nonlinear bio-heat transfer equation (BHTE). The images were generated for various antenna settings, and were meant to mimic thermal images obtained from MR imaging. The virtual source bases were determined according to equation (6). Increasing numbers of these linearly independent virtual source base vectors (1–9) were used to numerically optimize the temperature field using the nonlinear BHTE. The quality of the treatment was estimated as a function of this variable. The resulting temperature distributions were compared to the full ten-dimensional optimization.

3. Results

Table 2 lists the 1st, 5th and 10th linearly independent virtual source bases for the upper leg model. The virtual source bases are ranked in order from the most effective to least effective for tumor heating. This is seen qualitatively in figure 4, which displays heating of a central axial slice through tumor for these three predefined source configurations.

Six sets of optimizations were simulated: simulation (1) linear BHTE with fixed perfusion in the CT based thigh model; simulation (2) linear BHTE with fixed perfusion in the simplified thigh model; simulation (3) linear BHTE with fixed perfusion in the simplified thigh model where tumor is shifted 2.0 cm along the y direction; simulation (4) linear BHTE with fixed perfusion in the simplified thigh model where tumor is shifted 2.0 cm in both x and y directions; simulation (5) nonlinear BHTE with temperature-dependent perfusion in the real thigh model; and simulation (6) nonlinear BHTE with temperature-dependent perfusion in the simplified thigh model.

For simulation (1), figure 5 shows the optimized temperature rise distributions (using 37 °C as the boundary condition at the skin–bolus interface) at three axial (z) positions along the upper-leg model, for the full optimization (using all ten actual sources), using only the first five linearly independent virtual source base vectors, and using only the first four linearly independent virtual source base vectors in equation (6). Temperature distributions in the central slice ($z = 0.0$) are qualitatively similar, while temperature rise distributions at the two ends (especially $z = 3.6$ cm) are somewhat less so. Figure 6 compares the results obtained with the number of linearly independent virtual source base vectors: 10, 8, 6, 4, 2 and 1, for the central slice ($z = 0.0$). Note that when only one virtual source was used for the optimization, the numerical algorithm simply adjusts the total output power to meet the objective. For simulations (1) (left column in figure 7) and (5) (right column in figure 7), figure 7 provides the percentages of tumor and normal tissues that were heated to different temperature elevations when the first 10, 6, 5, 4 and 2 linearly independent virtual source base vectors were used. Since the major goal of this study is to explore the feasibility of using a smaller number of virtual sources to obtain a comparable optimal temperature distribution, the closer these curves are to the ten configuration result (full optimization), the better. Using at least five or six linearly independent virtual source base vectors yielded temperature distributions that were comparable to the full optimization for linear or nonlinear BHTE, respectively. Note further that the percentages of tumor and normal tissue heating are quite different for the cases of linear and nonlinear BHTE. The volume percentages of tumor and normal tissue having temperature ≥ 40 °C are greater for temperature-dependent perfusion. Figure 5–Figure 7 qualitatively illustrate the variation in tumor heating possible with different numbers of linearly independent virtual source base vectors. Figure 8 summarizes this variation quantitatively with an objective value J^* (see section 4, model uncertainties), and the difference of J^* values with respect to the reference J (full optimization) values as a function of the number of linearly independent virtual source base vectors used. These curves provide a quantitative view of how well the optimal results using the linearly independent virtual source base vectors determined from

mismatched models compare with the nominal model. As the number of linearly independent virtual source base vectors increases, both fixed perfusion (simulations (2)–(4)) and temperature-dependent perfusion (simulation (6)) simulations approach their reference simulations, i.e., simulation (1) for fixed perfusion and simulation (5) for temperature-dependent perfusion. The curves suggest that four linearly independent virtual source base vectors are sufficient to effectively optimize heating for this ten-antenna system.

Figure 9 summarizes the comparison for all points in the tumor that are at temperatures $\geq 43^\circ\text{C}$. The difference in the results decreases starting from four linearly independent virtual source base vectors. No less than 75% and 99% of the target tumor, for fixed perfusion cases and temperature-dependent perfusion cases, respectively, were heated to $\geq 43^\circ\text{C}$ when at least six virtual sources were used to optimize the treatment. Higher percentages of tumor volumes were heated to $\geq 43^\circ\text{C}$ when blood perfusion depends on temperature. Figure 10 summarizes the comparison for all points in the normal tissues that are at temperatures $\geq 41^\circ\text{C}$. These figures provide another perspective on how tumor and normal tissue heating trade off. The simulations converge to each other for ≥ 4 linearly independent virtual source base vectors, and higher percentages of normal tissue volumes were heated to $\geq 41^\circ\text{C}$ when blood perfusion depends on temperature.

Note that virtual source N is the eigenvector corresponding to the N th maximal eigenvalue of the averaged tumor matrix given in equation (6).

4. Discussion

The major goal of this study, approximating the heating pattern of a large number of physical antennas with a smaller number of pre-calculated linearly independent source configurations, i.e., virtual sources, appears to be feasible. From figure 5 and figure 8, it is clear that using as few as four to five linearly independent virtual source base vectors optimizes the temperature field in a manner comparable to the full optimization using all ten physical sources. From figure 8, the trend of the objective function values decreasing asymptotically, as the number of linearly independent virtual source base vectors increases, indicates that using a critical number of linearly independent virtual source base vectors leads to an approximately equivalent result to the full optimization. The success of this model reduction method allows researchers to build a ‘virtual source phased array’ that best treats each individual patient by simply adjusting a set of numerical parameters on the same physical antenna array.

Figure 7, Figure 9 and Figure 10 together show that this virtual source approach also works for cases where the blood perfusion depends on temperature elevation (Song *et al* 1984, Sekins *et al* 1984, Roemer *et al* 1985, Akyurekli *et al* 1997). Results from figure 9 and figure 10 also support that using a few linearly independent virtual source base vectors determined in the simplified patient model (see figure 1(b)) (or the simplified patient model with different tumor locations) lead to temperature distributions that are comparable to that from all physical sources. Thus, the proposed virtual source concept appears to be applicable in practical situations where the perfusion depends on temperature. The time reduction obtained from optimizing such a nonlinear BHTE was significant. The optimization time required using only the first four to five virtual sources was approximately 1/3 to 1/4 of that required for full optimization.

Another advantage of this approach is that these linearly independent virtual source base vectors can be determined in a simplified patient model (see figure 1(b)), which significantly reduces the time required to build an accurate, detailed patient model (see figure 1(a)) for treatment planning. More importantly, patients having tumors of similar size and position can share the same set of linearly independent virtual source base vectors, since they are not overly

sensitive to tumor shape. Therefore, the proposed model reduction method provides an efficient way (without the time expenditure required to build a patient-specific model) to build a flexible ‘virtual array’ that provides the most effective focused heating for patients with similar geometry and tumor location. Moreover, physicians can quickly build a simplified model like that shown in figure 1(b) to determine the linearly independent virtual source base vectors based roughly on patient CT scan images.

Figure 5 and Figure 6 illustrate the trade-off between maximizing tumor killing and minimizing normal tissue damage. It is observed that heat was re-distributed as the number of virtual sources increased; more tumor volume was heated, but, at the same time, more normal tissue volumes were heated on the opposite side of tumor. Also note that as the number of linearly independent virtual source base vectors increases, the proposed ten-antenna heating system, which is an extended design of the BSD-2000 SIGMA 30 system, tends to become more saturated to its full heating capacity. As shown in figure 9, the system asymptotically tends to heat 75% of the whole tumor to $\geq 43^{\circ}\text{C}$ when the perfusion is fixed, and to heat 99% when the perfusion depends on temperature. At the same time, as shown in figure 10, less than ~25% of normal tissues are above 41°C for fixed perfusion cases, and less than ~42.5% for temperature-dependent perfusion cases. Lastly, it was found that the peak normal tissue temperatures gradually decrease to a constant as the number of linearly independent virtual source base vectors increases (results not shown in figures).

5. Conclusions

The proposed reduced-order modeling approach works for practical EM hyperthermia treatment setup and is robust for model mismatch caused by measurement noise, geometry and position mismatch. Though the proposed model reduction approach is based on fundamental linear system theory, it is also demonstrated to work for the nonlinear case where blood perfusion depends on temperature elevation. For a patient upper-leg model heated using a 140 MHz cylindrical ten-antenna phased array applicator, which is a design extension of the BSD-2000 SIGMA 30 system, using just the first four to five linearly independent virtual source base vectors (magnitude and phase combinations for exciting the ten-antenna array) appears to provide temperature distributions that are comparable to those from the full optimization of all ten physical sources. For EM frequencies other than that tested here (140 MHz), further tests are required to ascertain the utility of the virtual source approach. The model order reduction method developed here will ultimately aid in facilitating real-time MR thermal image-guided focusing of heat in EM systems with a large number of heating sources.

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Figure 1.

(a) Electromagnetic segmentation model of upper leg as derived from patient CT scan showing anatomical structures (red for tumor, blue for bone, green for muscle and yellow for fat) inside ten-antenna cylindrical array. The antennas are evenly separated by 36° around a cylindrical surface of diameter = 23 cm and length = 27.5 cm. (b) Simplified electromagnetic segmentation model of tissue geometry (red for tumor and blue for muscle) inside the ten-antenna array. The simplified truncated cone model dimensions are as follows: length = 40 cm; larger cone base ellipse radii = 10.5 cm, 8.6 cm; smaller cone base ellipse radii = 8 cm, 6 cm. The tumor was assumed to be cylindrical, with dimensions: length = 10.0 cm, radius = 3.2 cm.

Figure 2.

A typical histogram of phase change distribution for the region-of-interest demarcated by the box (inset). The experiments were conducted on a cylindrical muscle equivalent phantom with MR images acquired perpendicular to the axis of the cylinder. The experimentally determined coefficient of $0.1 \text{ rad } ^\circ\text{C}^{-1}$ is used in this work to convert phase difference images into 2D temperature maps.

Figure 3.

Curves modeling perfusion-temperature relations in fat, muscle and tumor, attempting to mimic the trend observed in Song's experimental data. In developing these functions, we assumed that perfusion increases with temperature in all tissue, ranging from 30% below to 30% above the constant perfusion values in table 1.

Figure 4.

Effect of individual virtual sources on tumor heating. Out of ten linearly independent virtual sources computed based on the ten-antenna mini-annular-phased-array (figure 1(a)), only three are shown. Virtual sources are numbered according to their rank in average tumor heating, with one being the most efficient and ten the least efficient. Each figure was plotted for a constant total power (table 1 shows magnitude and phase configurations). The outermost ring is fat, surrounding the muscle region. The larger irregular object on the left side of the muscle region is tumor, and the smaller irregular object at the center is bone. The colored regions areas follows: red for ≥ 43 °C, yellow for ≥ 41 °C, light blue for ≥ 40 °C and blue for ≥ 39 °C.

Figure 5.

Simulation (1): best possible temperature elevation distributions at three different Z-locations, for ten linearly independent virtual source base vectors (left column), five linearly independent virtual sources (middle column), and four linearly independent virtual source base vectors (right column). The outermost ring is fat, surrounding the muscle region. The larger irregular object on the left side of the muscle region is tumor, and the smaller irregular object at the center is bone. The colored regions are as follows: red for ≥ 43 °C, yellow for ≥ 41 °C, light blue for ≥ 40 °C and blue for ≥ 39 °C.

Figure 6. Simulation (1): optimal temperature elevation distributions at the central slice ($z = 0.0$ cm) for linearly independent virtual source base vectors: 10, 8, 6, 4, 2 and 1. Geometry and labels are as in figure 5.

Figure 7.

Simulation (1): percentages of tumor/normal tissues' that are ' $\geq$ ' index temperature using the first 10 (x), 6 (o), 5 (+), 4 (Δ) and 2 (∇) linearly independent virtual source base vectors that maximize the average tumor temperature.

Figure 8.

The optimized objective values (J^*) and the difference with the reference objective values (J) (simulation (1) is the reference for fixed perfusion and simulation (5) is the reference for the temperature dependent perfusion), when different numbers of linearly independent virtual source base vectors are used.

Figure 9. The percentage of heated tumor ($T \geq 43^\circ\text{C}$) when different numbers of linearly independent virtual source base vectors are used.

Figure 10.

The percentage of heated normal tissues ($T \geq 41^\circ\text{C}$) when different numbers of linearly independent virtual source base vectors are used.

Table 1

Nominal property values (assumed for 140 MHz).

	Relative electric permittivity, $\epsilon_R, \epsilon_R = \frac{\epsilon}{\epsilon_0}$	Electrical conductivity σ (mho m ⁻¹)	Density ρ (kg m ⁻³)	Specific heat, C_p (J kg ⁻¹ K ⁻¹)	Thermal conductivity k (W m ⁻¹ °C ⁻¹)	Blood perfusion ω_b (kg m ⁻³ s ⁻¹)
Blood	-	-	-	3770	-	-
Bone	10	0.05	1600	1300	0.40	0.0
Fat	4.5	0.06	880	2387	0.23	1.1
Muscle	58.8	0.63	1050	3639	0.50	3.6
Tumor	59	0.65	1050	3639	0.50	1.8
Water	81	0.0002	996	4178	0.61	-

Table 2

Linearly independent virtual sources.

	Virtual source 1		Virtual source 5		Virtual source 10	
	Magnitude	Phase (degrees)	Magnitude	Phase (degrees)	Magnitude	Phase (degrees)
Antenna 1	0.33	0	0.39	0	0.11	0
Antenna 2	0.14	-8	0.09	-62	0.76	-225
Antenna 3	0.17	-310	0.38	-140	0.26	-352
Antenna 4	0.17	-170	0.30	66	0.33	-297
Antenna 5	0.07	-234	0.12	99	0.33	-170
Antenna 6	0.20	-275	0.64	-162	0.09	-180
Antenna 7	0.23	-46	0.32	91	0.21	-79
Antenna 8	0.81	-351	0.15	-72	0.03	-219
Antenna 9	0.15	-98	0.04	-99	0.065	-292
Antenna 10	0.16	-87	0.17	-79	0.24	-136