3D-specific absorption rate estimation from high-intensity focused ultrasound sonications using the Green's function heat kernel

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Purpose: To evaluate a numerical inverse Green's function method for deriving specific absorption rates (SARs) from high-intensity focused ultrasound (HIFU) sonications using tissue parameters (thermal conductivity, specific heat capacity, and mass density) and three-dimensional (3D) magnetic resonance imaging (MRI) temperature measurements.

Methods: SAR estimates were evaluated using simulations and MR temperature measurements from HIFU sonications. For simulations, a “true” SAR was calculated using the hybrid angular spectrum method for ultrasound simulations. This “true” SAR was plugged into a Pennes bioheat transfer equation (PBTE) solver to provide simulated temperature maps, which were then used to calculate the SAR estimate using the presented method. Zero mean Gaussian noise, corresponding to temperature precisions between 0.1 and 2.0°C, was added to the temperature maps to simulate a variety of *in vivo* situations. Experimental MR temperature maps from HIFU sonications in a gelatin phantom monitored with a 3D segmented echo planar imaging MRI pulse sequence were also used. To determine the accuracy of the simulated and phantom data, we reconstructed temperature maps by plugging in the estimated SAR to the PBTE solver. In both simulations and phantom experiments, the presented method was compared to two previously published methods of determining SAR, a linear and an analytical method. The presented numerical method utilized the full 3D data simultaneously, while the two previously published methods work on a slice-by-slice basis.

Results: In the absence of noise, SAR distribution estimates obtained from the simulated heating profiles match closely (within 10%) to the initial true SAR distribution. The resulting temperature distributions also match closely to the corresponding initial temperature distributions (<0.2°C RMSE). In the presence of temperature measurement noise, the SAR distributions have noise amplified by the inverse convolution process, while the resulting temperature distributions still match closely to the initial “true” temperature distributions. In general, temperature RMSE was observed to be approximately 20–30% higher than the level of the added noise. By contrast, the previously published linear method is less sensitive to noise, but significantly underpredicts the SAR. The analytic method is also less sensitive to noise and matches SAR in the central plane, but greatly underpredicts in the longitudinal direction. Similar observations are made from the phantom studies. The described numerical inverse Green's function method is very fast — at least two orders of magnitude faster than the compared methods.

Conclusion: The presented numerical inverse Green's function method is computationally fast and generates temperature maps with high accuracy. This is true despite generally overestimating the true SAR and amplifying the input noise. © 2018 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12978>]

Key words: Green's function, high-intensity focused ultrasound, MR-guided FUS, specific absorption rate

1. INTRODUCTION

Patient-specific treatment planning, monitoring, and control are important areas where improvements must be made before high-intensity focused ultrasound (HIFU) treatments can be universally accepted in the clinic. Thermal modeling is a critical component for these different treatment steps, and it is often done utilizing the Pennes bioheat transfer equation¹ (PBTE). For accurate thermal modeling using PBTE, clinicians need accurate predictions of patient-specific *in vivo* tissue thermal and acoustic

properties, such as the thermal conductivity and diffusivity, tissue perfusion, acoustic absorption, speed of sound, and specific absorption rate (SAR).^{2–8} While ultrasound transducer characteristics and power are important factors, they are insufficient to accurately determine the actual *in vivo* SAR in three dimensions, due to large variations in tissue thermal and acoustic properties between different tissue types and different patients. Three-dimensional (3D) MR thermometry provides a robust set of data by which the full spatial extent of the SAR magnitude can be determined.

SAR (measured in W/kg) is a measurement of the power absorbed per mass and is closely related to the heat deposition term, Q , of the PBTE, given as:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T - w c (T - T_{ar}) + Q \quad (1)$$

where ρ = mass density of tissue (kg/m³), c = specific heat of tissue (J/kg/°C), T and T_{ar} = tissue and arterial blood temperature (°C), k = thermal conductivity (W/m/°C), w = Penes blood perfusion constant (kg/m³/s), and Q = heat deposition per unit volume (W/m³). SAR relates to Q by:

$$SAR = \frac{Q}{\rho}. \quad (2)$$

Any estimation of SAR will therefore accompany a determination of Q if the tissue mass density is known.

To estimate Q from MR thermometry data, Roemer et al.² proposed a method where a linear fit to the first few dynamic time points of heating is performed under the assumption that losses to conduction and blood flow are minimal during this time. This assumption was shown to be true for microwave and ultrasound sonications for durations of tens of seconds. A more accurate analytical method for estimating Q from HIFU MR thermometry data has been proposed by Dillon et al.^{5,7,9,10} The method fits the analytical temperature solution of a one-dimensional (1D) radial Gaussian heating pattern to temperature data and evaluates the initial slope of the analytical solution. Since it is based on a 1D radial Gaussian, axial conduction is ignored. The accuracy is greatest for the central part of the focal spot in the axial direction (i.e., along the long axis of the focal spot), and accuracy is decreased as the distance from the center increases. In this method, an estimate of the thermal conductivity, k , is obtained simultaneously with the estimate for Q .

In this study, we derive and present a numerical inverse Green's function method for determining Q in three dimensions using the heat kernel, or Green's Function. The method is evaluated using both simulations and phantom data. 3D temperature maps are simulated using SAR from the hybrid angular spectrum ultrasound simulation method and PBTE, and 3D MR temperature maps are obtained during HIFU sonications in a tissue-mimicking gelatin phantom. The presented numerical method is further compared to the methods of Roemer and Dillon mentioned above. The main advantage of the described numerical method over the previously published methods are its speed (at least two orders of magnitude faster) and that it acts on the full 3D data, as compared to the previous methods which performs fittings on a slice-by-slice basis.

2. METHODS

2.A. SAR determination methods

In all three methods described below (Roemer's linear, Dillon's analytical, and the presented numerical method), it is assumed that Q does not vary with time (i.e., Q is a step

function) and is only spatially variable. Furthermore, the linear and analytical methods estimate SAR by fitting the temperature data to known functions. Each method assumes that in the instant after heating begins, conduction and perfusion are negligible compared to heat deposition. Taking this time to be the time $t = 0$, Eqs. (1) and (2) give:

$$SAR = c \left. \frac{\partial T}{\partial t} \right|_{t=0^+} \quad (3)$$

By contrast, however, the numerical inverse Green's function method relies only on Eq. (2) to estimate SAR since it does not provide a closed-form expression for Q .

2.A.1. Linear method

The linear method extends Eq. (3) by assuming there is no heat conduction or blood perfusion at any time during the heating. The solution to Eq. (1) is therefore:

$$T = At \quad (4)$$

where $A = Q/\rho c$. Temperature data is then dynamically fitted to this model using subsequent time points to find A . Once found, SAR is given by:

$$SAR = cA. \quad (5)$$

2.A.2. Analytical model

A full description of the analytical method can be found in the literature,^{5,7,9} and only a brief description as background is given here. This model ignores axial conduction and perfusion when the axial-to-lateral beam width aspect ratio is greater than 2 (a finding by Kress and Roemer¹¹). It then assumes the HIFU beam's Q is given in cylindrical coordinates by:

$$Q = 2\alpha I_0 \cdot \exp\left(-\frac{r^2}{\beta}\right) \quad (6)$$

where α = ultrasound absorption coefficient (Np/m/MHz), I_0 = ultrasound intensity (W/m²), and β = ultrasound Gaussian variance (m²). Assuming the temperature is circularly symmetric, the azimuth part of the Laplacian can be ignored, making Eq. (1):

$$\rho c \frac{\partial T}{\partial t} = \frac{k}{r} \frac{\partial}{\partial r} \left(r \frac{\partial T}{\partial r} \right) + 2\alpha I_0 \cdot \exp\left(-\frac{r^2}{\beta}\right). \quad (7)$$

The solution to Eq. (7) is given by¹²:

$$T(r, t) = \int_0^t \frac{2\alpha I_0}{\rho c (1 + 4\kappa\tau/\beta)} \exp\left(-\frac{r^2}{4\kappa\tau + \beta}\right) d\tau \quad (8)$$

where κ = thermal diffusivity (m²/s). Experiments must be done to determine the values of I_0 , α , and β . Once found, SAR is given by differentiating Eq. (8):

$$SAR = cC \cdot \exp\left(-\frac{r^2}{\beta}\right) \quad (9)$$

where $C = 2\alpha I_0/\rho c$. Kress and Roemer¹¹ further extended this solution to include perfusion effects, which affect accuracy positively and has been further explored by Dillon et al.⁷

2.A.3. Numerical inverse Green's function method

The numerical inverse Green's function method presented here includes perfusion and conduction effects. By Green's formula for differential equations, the solution to the PBTE is of the form of¹³:

$$T = T_0 + \frac{1}{\rho c} \int_0^\infty \int \int \int_{\mathbf{R}^3} G(x, y, z, t; x', y', z', t') (Q(x', y', z') + wcT_{ar}) d\mathbf{x}' dt' \quad (11)$$

where T_0 and G solve the respective problems:

$$\begin{cases} \rho c \frac{\partial T_0}{\partial t} - k \nabla^2 T_0 + wc(T_0 - T_{ar}) = 0 \\ T_0(x, y, z, 0) = f(x, y, z) \end{cases} \quad (12)$$

$$\begin{cases} \rho c \frac{\partial G}{\partial t} - k \nabla^2 G + wc(G - T_{ar}) = \delta(\mathbf{x} - \mathbf{x}') \delta(t - t') \\ \lim_{t \rightarrow t'} G(x, y, z, t - t') = 0, \quad \mathbf{x} \neq \mathbf{x}' \end{cases} \quad (13)$$

where δ denotes the Dirac delta-function. Both problems can be solved through use of the spatial Fourier transform. The solution to Eq. (12) (see Appendix for details) is:

$$T_0 = \int \int \int_{\mathbf{R}^3} K(x - x', y - y', z - z', t) f(x', y', z') d\mathbf{x}', \quad (14)$$

where K is the heat kernel, given by:

$$K = \left(\frac{1}{2\sqrt{\pi \kappa t}} \right)^3 \exp\left(-\frac{x^2 + y^2 + z^2}{4\kappa t}\right) \exp\left(-\frac{w}{\rho} t\right). \quad (15)$$

Likewise, the solution to Eq. (13) is given by:

$$G = \theta(t - t') \cdot K(x - x', y - y', z - z', t - t'), \quad (16)$$

where θ denotes the Heaviside function.

The nature of the Heaviside function means that in Eq. (11), the temporal part of the integral need only span 0 to t . Thus, using Eqs. (14) and (16), (11) can be written in the form of a sum of convolutions:

$$T = (f^{sp} * K) + \frac{1}{\rho c} ((Q + wcT_{ar}) * K) \quad (17)$$

where sp denotes spatial convolution only.

To solve Eq. (17) for Q , it is necessary to use the convolution theorem to deconvolve each element. Taking the Fourier Transform of both sides and rearranging gives:

$$\frac{\hat{Q}}{\rho c} = \frac{\hat{T} - \hat{f}\hat{K} - (w/\rho)\mathcal{F}(T_{ar} * K)}{\int_0^t \hat{K}(k_x, k_y, k_z, \tau) d\tau}. \quad (18)$$

Q was factored out of the integral on the RHS because, as stated above, it is assumed to be constant in time. Using Eq. (15), we find the Fourier Transform of the heat kernel is: $\hat{K}(k_x, k_y, k_z, t) = \exp(-4\pi^2 \kappa t |\mathbf{k}|^2 - w/\rho)$ such that the denominator of the RHS of Eq. (18) is therefore:

$$\int_0^t \hat{K} d\tau = \left(\frac{1}{4\pi^2 \kappa |\mathbf{k}|^2 + w/\rho} \right) (1 - \exp(-4\pi^2 \kappa t |\mathbf{k}|^2 - w/\rho)), \quad (19)$$

which approaches zero as the magnitude of frequency approaches infinity. This implies that Q 's transform does not vanish at infinity.

To avoid the vanishing problem, data from Eq. (18) should be windowed. However, since MRI data is finite in k-space, it is effectively windowed already and therefore requires no additional manipulation to generate Q .

Once Q is obtained, SAR is given by:

$$SAR = c\mathcal{F}^{-1} \left(\frac{\hat{T} - \hat{f}\hat{K} - (w/\rho)\mathcal{F}(T_{ar} * K)}{\int_0^t \hat{K}(k_x, k_y, k_z, \tau) d\tau} \right). \quad (20)$$

For the simulations and phantom experiments performed in this study, w is 0, which simplifies Eq. (20) to:

$$SAR = 4\pi^2 \kappa c \mathcal{F}^{-1} \left(\frac{\hat{T} - \hat{f} \exp(-4\pi^2 \kappa t |\mathbf{k}|^2)}{1 - \exp(-4\pi^2 \kappa t |\mathbf{k}|^2)} |\mathbf{k}|^2 \right). \quad (21)$$

Note that in Eq. (21), t is taken to be the time since the heating began in seconds.

2.B. Simulation study

The simulation study was performed by simulating the heating that would occur from a realistic 3D Q distribution in a phantom with realistic acoustic and thermal properties. The sequence of realistic 3D temperatures created in this simulation, were then used to determine Q based on the three methods described above. The original Q pattern is referred to as the "true" Q and the sequence of 3D temperatures as the "true" temperatures.

The starting Q distribution ("true" Q) was obtained by using the hybrid angular spectrum (HAS) ultrasound simulation method¹⁴ to calculate the Q distribution for a 1-MHz, 256-element phased-array HIFU transducer at a spatial resolution of 0.5-mm isotropic. HAS is a full-wave simulation method that takes into account US refraction, absorption, and first-order reflection. The temporal sequence of "true" 3D temperature distributions was obtained using the "true" Q in a finite difference time domain (FDTD) implementation of the PBTE, with simulation parameters as shown in Table I.

To mimic the phantom study (see below) as closely as possible, the four-dimensional (4D) temperatures were converted

TABLE I. Parameters used in the simulation study, chosen in the range of soft tissues,¹⁷ and parameters as given in Ref. [18] for the tissue-mimicking gelatin phantom.

Parameter	Simulation study	Phantom study
Mass density (kg/m ³)	1000	1067
Specific heat (J/(kg K))	3586	3673
Thermal conductivity (W/(m K))	0.40	0.56
Voxel size (mm)	0.5 × 0.5 × 0.5	1.15 × 1.15 × 2.5
Tissue speed of sound (m/s)	1553	1553
Ultrasound attenuation (Np/(cm MHz))	0.06	0.06
Temporal resolution (s)	4.774	4.774
HIFU sonication duration (s)	28.644	28.644
Field of view (mm)	81.5 × 81.5 × 38.5	147 × 96 × 30

to MR phase using the proton resonance frequency shift (PRFS) equation.^{15,16} The 4D time series of the temperature-induced phase change was added to a 4D complex image of a cylinder, where the cylinder mimics the phantom used in the phantom study. The cylinder had a constant magnitude of 1 and a constant phase of $\pi/4$ (where the values of 1 and $\pi/4$ were arbitrarily chosen). To mimic different noise levels in the MR temperatures, the complex images were Fourier transformed to the k-space domain where zero-mean Gaussian noise (using Matlab's *randn()*-function) was added independently to each element of the real and the imaginary channels. The noise amplitude was adjusted so that when the complex k-space data was inverse-Fourier transformed back to image-space and temperatures were calculated using the PRFS equation, the standard deviation (SD) through time (calculated using Matlab's *std()*-function) of an unheated background area of the cylinder was approximately 0, 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, and 2.0°C.

Using a sequence of “true temperatures” with varying amounts of noise added, the three methods of determining Q are applied to obtain an estimate of Q for each method, for each noise level, and for different time windows of temporal data. To investigate the behavior of the implemented algorithm to different amounts of data, Q patterns were generated using different time windows of temporal data as input, including between 1 and 6 dynamic time points, when calculating the kernel K in Eq. (19). The six different Q 's generated with different amounts of data were also averaged to improve the SNR. To evaluate the effect of the spatial resolution used, this was repeated for 0.25-mm and 0.10-mm isotropic resolutions as well. 3D temperature sequences obtained using these Q estimates in the PBTE are then compared against the original “true temperatures.”

2.C. Phantom study

The phantom was constructed of tissue-mimicking gelatin (125-bloom ballistics gelatin, Vyse Gelatin Co., Schiller Park,

IL, USA) in an acrylic cylinders (12-cm inner diameter, 15-cm height).¹⁸ HIFU sonications were performed using an MR-compatible phased-array ultrasound transducer (256 elements, 1-MHz frequency, 13-cm radius of curvature, focal spot size full width at half maximum $2 \times 2 \times 8$ mm, Imasonic, Voray-sur-l'Ognon, France) with accompanying hardware and software for mechanical positioning and electronic beam steering (Image Guided Therapy, Pessac, France). The transducer was coupled to the phantom with a bath of deionized and degassed water. HIFU was applied for a duration of 28.644 s (corresponding to 6 dynamic 3D MR temperature maps, see below) with powers of 6, 9, 19, and 40 W. The corresponding four temperature maps are considered “truth” for the further comparison of the three described methods of obtaining Q .

All MR imaging was performed on a 3T MRI scanner (TIM Trio, Siemens Medical Solutions, Erlangen, Germany). A 3D gradient recalled echo (GRE) pulse sequence with segmented (i.e., multishot) echo planar imaging (EPI) readout was used for all MR thermometry. Imaging parameters included TR/TE = 22/11 ms, field of view = $147 \times 96 \times 30$ mm, resolution = $1.15 \times 1.15 \times 2.5$ mm, flip angle = 15° , readout bandwidth = 752 Hz/pixel, echo train length = 7, and acquisition time per 3D volume = 4.774 s. All MR data were zero-filled interpolated to 0.5-mm isotropic voxel spacing to minimize partial volume effects.¹⁹ An in-house-built RF receive-only single-channel loop coil was used for signal detection. The precision of the MRTI was estimated by measuring the mean and SD of the SD-through-time of an unheated background area and were $0.158 \pm 0.022^\circ\text{C}$, $0.159 \pm 0.021^\circ\text{C}$, $0.159 \pm 0.022^\circ\text{C}$, and $0.163 \pm 0.022^\circ\text{C}$ for the 6, 9, 19, and 40 W cases, respectively.

2.D. Error comparisons

For both the simulation and phantom studies, accuracy was assessed by comparing the temperature predictions created by inserting the determined SAR distributions in the PBTE with the “true” input temperature distributions themselves. Accuracy was defined as the voxel-wise root mean square error (RMSE) for all points where the original “true” temperature rise was above a chosen threshold. For all simulation studies and the 19 and 40 W phantom experiments, the threshold chosen was 6°C (the point at which significant thermal dose would start to accumulate, assuming a starting temperature of 37°C ²⁰). For the 6 and 9 W phantom experiments, the threshold chosen was 2.5°C to provide enough voxels for comparison. Precision, which was calculated for the phantom “true” data, was defined as the spatial mean of the SD through time in a background ROI which did not experience any heating.

The full width at half maximum (FWHM) was calculated for all Q and temperature maps, for both the simulation and phantom studies. The FWHM was found by linear interpolation within the (zero-filled interpolated) voxels.

All image reconstruction and simulations were performed using Matlab (R2017a, MathWorks, Natick, MA).

3. RESULTS

For consistency in comparisons for all studies, the Q values are presented and plotted in terms of Q_{rel} , which is defined as the obtained Q normalized by the input power.

3.A. Simulation study

3.A.1. Numerical inverse Green's function method evaluation

Figures 1(a) and 1(b) show line plots of Q_{rel} through two orthogonal views centered at the voxel of maximum Q_{rel} , generated using different amounts of temporal data (ranging from using just the first temporal dynamic, to using all six temporal dynamics) when calculating the kernel K in Eq. (19) for the noiseless case. Using the average of the six different Q_{rel} (to improve the SNR) is also shown. It can be seen that the smallest errors occur for the case where just the first dynamic is used to estimate Q_{rel} . The difference between the use of 2 and 6 temporal dynamics is very small. Figure 1(c) further shows the temporal temperature profiles for the voxel with maximum temperature rise, after inputting the Q_{rel} from Figs. 1(a) and 1(b) into PBTE, i.e., the noiseless case and including varying numbers of dynamic time frames when estimating the kernel K in Eq. (19). Figure 1(c) also shows the single-voxel error for the hottest voxel compared to truth as a function of temporal dynamics. Figure 1(d) shows the RMSE for all voxels with temperature rise over 6°C for each temporal dynamic, and the average of the 6 dynamics. It can be seen that the maximum single-voxel error is below 1.0°C in all cases, and that the RMSE is below 0.7°C in all cases. Table II lists the total RMSE for all voxels in the 4D temperature map which had a temperature rises above 6°C , compared to simulated “truth,” and it can be seen that the best accuracy is achieved for the 1 dynamic case and the

FIG. 1. Simulation of Q_{rel} for the numerical method (Green's function) including different number of dynamics in the estimation process, for the case of no added noise. (a) and (b) Line plots of Q_{rel} through X and Z, respectively, at position of maximum Q_{rel} . (c) Temporal temperature evolution of voxel experiencing maximum temperature rise, using Q_{rel} from (a) and (b) in the PBTE. Dotted lines show temperature error compared to truth. (d) RMSE for all voxels with a temperature rise greater than 6°C . [Color figure can be viewed at wileyonlinelibrary.com]

accuracy decreases when later dynamics are used to estimate Q_{rel} . Fig. S1 shows the corresponding data for all five different noise levels, and for the three different spatial resolutions (0.5, 0.25, and 0.1 mm isotropic) investigated. In the noiseless cases, the best accuracy is achieved when using 1 temporal dynamic, but as noise is added to the simulation, using the average Q_{rel} results in smaller RMSEs.

Figure 2 shows similar data as in Fig. 1, but for different simulated noise levels, as described above. For all data in Fig. 2, the six Q patterns created using different amount of temporal data were averaged. Figures 2(a) and 2(b) show line plots of Q_{rel} through two orthogonal views centered at the voxel of maximum Q_{rel} . It can be seen that for all noise cases, Q itself is fairly noisy, but the 0.1°C case follows the true Q_{rel} reasonably closely. Figure 2(c) shows the temporal temperature profiles for the voxel with maximum temperature rise, using the noisy distributions of Q_{rel} [Figs. 2(a) and 2(b)] in the PBTE. Figure 2(c) also shows the corresponding single-voxel error over time. Figure 2(d) shows the RMSE for all voxels with temperature rise over 6°C for each temporal dynamic. For the single-voxel error, the noise SD of 0.1 and 0.3°C cases have similar accuracy, but taking a larger ROI into account as in the RMSE shown in Fig. 2(d), it can be seen that the lowest noise is the most accurate and higher noise levels decrease the temperature measurement accuracy as expected. For all noise cases, the single-voxel error is below 2°C and the RMSE is below 2.5°C . Table II further lists the RMSE for all voxels with temperature rise above 6°C for all voxels in the 4D temperature map, compared to simulated “truth,” for all eight noise cases. Again, it can be seen that higher noise levels result in reduced temperature measurement accuracy, with the RMSE generally being 20–30% higher than the level of the added noise.

3.A.2. Comparisons with other methods

Figure 3 shows the profiles of Q_{rel} through two orthogonal directions for simulated “truth” and the three methods being compared, for noise levels of 0.0, 0.2, and 0.5°C . It can be seen that the linear and analytical methods, which use data fitting, are relatively noise free in all cases, whereas the numerical method is considerably noisier. Figure 4 shows two orthogonal views of Q_{rel} images for truth and the three different methods for noise SD levels of 0.0, 0.2, and 0.5°C . Again, the increasing noise level in the Q_{rel} estimate for the numerical method can be observed, while the linear and especially the analytical methods visually look less affected by the increasing noise levels. The FWHM values for the estimated Q_{rel} are shown in Figs. S1(a)–S1(c), where it can be seen that the analytical solution performs best in-plane, where the numerical solution underestimates (more so for higher noise levels) and the linear solution overestimates the width. For the z-direction (along the long axis of the FUS beam), the linear method performs the best, with the analytical method underestimating the beam width. The numerical solution again performs well for low noise levels.

TABLE II. Temperature RMSE for all simulation and phantom experiments. For simulations and the 19 and 40 W phantom studies, the RMSE was calculated for all voxels with a temperature rise $>6^{\circ}\text{C}$ in "truth". For the 6 and 9 W phantom studies, the RMSE was calculated for all voxels with a temperature rise $>2.5^{\circ}\text{C}$ in "truth". *Same data as in Fig. 1. **Same data as in Fig. 2 (for numerical method), and Figs. 5 and 6 (for all three compared methods). ***Same data as in Figs. 9 and 10. ****The high error for Noise SD = 2.0°C is the result of noise voxels away from the focal spot making its way into the error comparison. If the error comparison is confined to a $15 \times 15 \times 30$ voxel region just around the focal spot, hence limiting the number of noise voxels, the RMSE is 2.64, 3.25, and 3.05°C for the three methods, respectively.

Simulated data								
	1 dynamic	2 dynamics	3 dynamics	4 dynamics	5 dynamics	6 dynamics		
Numerical method * (noise SD = 0.0°C)	0.09°C	0.15°C	0.19°C	0.21°C	0.22°C	0.23°C		
	Noise SD = 0.0°C	Noise SD = 0.1°C	Noise SD = 0.2°C	Noise SD = 0.3°C	Noise SD = 0.4°C	Noise SD = 0.5°C	Noise SD = 1.0°C	Noise SD = 2.0°C ****
Numerical method** (averaged dynamics)	0.18°C	0.22°C	0.29°C	0.38°C	0.49°C	0.63°C	1.35°C	4.89°C
Linear method	0.83°C	0.81°C	0.89°C	0.98°C	0.87°C	1.17°C	1.69°C	6.01°C
Analytical method	0.29°C	0.32°C	0.35°C	0.50°C	0.58°C	0.77°C	1.53°C	5.91°C
Phantom data**								
			6 W		9 W		19 W	40 W
Numerical method (averaged dynamics)			0.16°C		0.22°C		0.48°C	0.71°C
Linear method			0.23°C		0.36°C		0.49°C	1.21°C
Analytical method			0.19°C		0.28°C		0.30°C	0.55°C

FIG. 2. Simulation of Q_{rel} for the numerical method (Green's function) for different levels of added noise. (a) and (b) Line plots of Q_{rel} through X and Z, respectively, at position of maximum Q_{rel} . (c) Temporal temperature evolution of voxel experiencing maximum temperature rise using Q_{rel} from (a) and (b) in the PBTE. Dotted lines show temperature error compared to truth. (d) RMSE for all voxels with a temperature rise greater than 6°C , for each dynamic time point. [Color figure can be viewed at wileyonlinelibrary.com]

The temperature vs time profiles for the hottest voxels for the three methods for noise levels of 0.0, 0.2, 0.4, and 1.0°C are shown in Fig. 5. In Fig. 5, the RMSE for all voxels with a temperature rise greater than 6°C for each dynamic is also shown (dotted lines). The analytical method can be seen to have the most accurate single-voxel temperature profiles, whereas the numerical method overestimates and the linear method underestimates the temperatures. Taking a larger ROI into account as in the RMSE measure, the numerical and

FIG. 3. Simulation of Q_{rel} for truth, numerical, linear, and analytical methods, for the cases of noise SD = 0°C (a and b), 0.2°C (c and d) and 0.5°C (e and f). The line plots are through the position of maximum Q_{rel} in X (a, c, and e) and in Z (b, d, and f). [Color figure can be viewed at wileyonlinelibrary.com]

analytical methods perform similarly, whereas the error for the linear method is greater. Two orthogonal views of the temperature image at the hottest time for the three methods and three noise levels (noise SD = 0.0, 0.2, and 0.5°C) are shown in Fig. 6. Table II lists RMSE for all voxels with temperature rise over 6°C in each of the 4D temperature maps for the three methods and all eight noise levels. As expected, the RMSE increases with increasing noise. The numerical method has slightly lower RMSE than the analytical method

FIG. 4. Simulation of Q_{rel} for the three methods being compared, showing two orthogonal views (X–Y plane and X–Z plane, respectively) for different levels of added noise. (a), (b), and (c) corresponds to noise SD of 0.0, 0.2, and 0.5°C, respectively. In each case, the first column shows truth, the second column the numerical method, the third column the linear method, and the fourth column the analytical method. The X–Y planes have been zoomed in to better show details. [Color figure can be viewed at wileyonlinelibrary.com]

for all noise levels, and the linear method experiences larger RMSEs in general. The FWHM of all temperature maps are shown in Figs. S1(d)–S1(f). In-plane, the numerical and analytical methods perform the best, with the linear method overestimating the width. Through-plane, the numerical method performs best, with the analytical and linear methods under- and overestimating the beam width, respectively.

3.B. Phantom study

Results from the phantom heating study are shown in Figs. 7–10. Figure 7 shows line plots through x and z of Q_{rel} for the numerical, linear and analytical methods that are obtained from the 4D MR temperature measurements. Transverse and sagittal images of Q_{rel} for the three methods are

FIG. 5. Simulation of temperature rise for truth and the three methods being compared for different levels of added noise. (a)–(d) corresponds to noise SD of 0.0, 0.2, 0.4, and 1.0°C, respectively. Dotted lines show RMSE for all voxels with a temperature rise greater than 6°C. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 6. Simulation of temperatures for Truth and the three methods being compared, showing two orthogonal views (X–Y plane and X–Z plane, respectively) for different levels of added noise of 0°C (a), 0.2°C (b), and 0.5°C (c). In each case, the first column shows truth, the second column the numerical method, the third column the linear method, and the fourth column the analytical solution. The X–Y planes have been zoomed in to better show details. [Color figure can be viewed at wileyonlinelibrary.com]

shown in Fig. 8. Figure 9 shows temporal plots for the hottest voxel of the temperature maps obtained from using the estimated Q_{rel} in the PBTE, compared to the directly measured (“true”) temperature values. In Fig. 9, the RMSE error for all voxels above the above-mentioned threshold (2.5°C for 6 W and 9 W, and 6°C for 19 W and 40 W) for all dynamics are also shown (dotted lines), and Table II lists the total RMSE for each 4D temperature map. Fig. 10 shows two orthogonal views of the corresponding temperature maps at the hottest time for the three methods compared to the originally measured “true” distribution for the four power levels. The FWHM of all Q_{rel} and temperature maps are shown in Fig. S2.

Reconstruction time to estimate Q_{rel} for the phantom heating using the numerical method was measured to be 3.4 s, for the linear method 1363 s, and for the analytical method 329 s. All tests were performed on nonoptimized Matlab code using a networked computer server (2.4 GHz Intel Xeon, Redhat CentOS, 95 Gb RAM).

4. DISCUSSION

In this work, we have derived and presented a numerical inverse Green’s function method that can be used to noninvasively estimate the *in vivo* SAR pattern from HIFU sonications. The main advantage of the described method is its speed and the fact that it estimates SAR from full 3D data. The numerical method is not very memory intensive and at least two orders of magnitude faster than the previously published methods. This can potentially allow SAR to be calculated in real time in an intraoperative setting on a moderate

FIG. 7. Phantom data of Q_{rel} for the three methods being compared, as determined from MRTI data with different applied FUS power. (a)–(d) show line plots through X (top row) and Z (bottom row) for FUS powers of 6 W, 9 W, 19 W, and 40 W, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

computer workstation, significantly aiding in patient-specific simulations for treatment planning, and for monitoring and control purposes. The described method also estimates SAR from full 3D temperature data, as opposed to subsequently performing fitting on 2D planes as the previously described methods. This greatly improves the accuracy of the SAR estimates in the through-plane direction, i.e., perpendicular to the FUS beam. The fact that the algorithm does not have to loop over multiple 2D planes is further one of the reasons it is computationally faster than the compared methods.

Because the Green's function method essentially deconvolves the Gaussian blurring of heat conduction, very

accurate SAR estimations can be made, as seen in Fig. 4(a) where, in the noiseless case, the numerical method is capable of estimating even the FUS grating lobes. For low values of noise (high SNR) in the simulation study, the SAR patterns derived from the numerical method were found to more closely approximate the true SAR distribution, especially in the through plane direction. However, the deconvolution makes the method very sensitive to noise in the measured temperature distribution, as seen in Figs. 4(b) and 4(c). However, in both the simulations and phantom studies, it was shown that temperature maps created using the estimated SAR from the presented numerical method were as accurate as those created using SAR from the previously most accurate analytical method. This was true despite the noise amplification in the estimated SAR maps.

The simulation study showed that the numerical method is the most accurate when temperature maps from dynamics 1 and 2 close to the beginning of the sonication (i.e., using small temporal backward propagations) are used, Figs. 1(a), 1(b), and Table S1. It was further shown that, even though the temporal backward propagation (deconvolution) of the Green's function amplifies the noise from each of the original temperature maps [seen, e.g., in Figs. 2(a) and 2(b), and 4(b) and 4(c)], application of the PBTE results in temperature maps that are close to the original temperature maps when using the obtained (noisy) Q (seen, e.g., Table II). For noisy input data, it was shown that improved accuracy could be obtained by averaging the estimated Q 's from multiple dynamic time points, Table S1. It can also be seen that the

FIG. 8. (a)–(d) Phantom data showing two orthogonal views (X–Y plane and X–Z plane, respectively) of Q_{rel} for the three methods being compared, as determined from MRTI data with applied FUS powers of 6 W, 9 W, 19 W, and 40 W, respectively. The X–Y planes have been zoomed in to better show details. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 9. Phantom data of temperature rise for truth and the three methods being compared, as determined from MRTI data with different applied FUS power.

(a)–(d) show plots of the voxel with largest temperature rise for FUS powers of 6 W, 9 W, 19 W, and 40 W, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

accuracy increases with increased spatial resolution, where it should be noted that the temperature SD through time is the same for all three resolutions. In real MRI data, the fact that higher resolution leads to lower SNR for a given sampling time would be superimposed on these results.

For the single hottest voxel plotted in Fig. 5, the analytical method performs the best while the numerical method generally overestimates the temperatures and the linear method underestimates them. This agrees with the in-plane (i.e., x – y plane) FWHM data presented in Fig. S1. The numerical method creates narrower Q patterns (smaller FWHM) in most cases, which results in narrower temperature distributions, which, in turn, create slightly overestimated maximum temperature rises since the thermal conductivity is fixed. For the linear method, the FWHM of Q_{rel} is generally overestimated, creating temperature estimates that are too wide and hence

underestimate the maximum temperature rise. The analytical method, which fits a 2D radial Gaussian and is most accurate for the center of the focal spot, performs very well for the in-plane FWHM. In the through-plane z -axis (along the HIFU beam) direction, however, the analytical method consistently underestimates the FWHM, while the numerical and linear methods perform better. While the analytic method is very accurate for the single hottest voxel in the center of the focal spot (Fig. 5) when a larger volume is taken into account, its RMSE is larger than that of the numerical method (Table II). Figure 3(a) and Fig. S1(c) further demonstrate that the numerical method, which takes the full 3D temperature map into account rather than performing fits on individual 2D slices as in the analytical method, is better at estimating Q away from the very central slice positions.

Like the simulation study, the phantom study shows that the numerical method creates noisier Q estimates when the SNR (in this case the temperature-rise to noise ratio) is lower, such as for the 6 W experiment, Figs. 7(a) and 8(a). When the SNR (or temperature-rise to noise ratio) increases for the higher power sonications, the noise in the Q estimate also decreases accordingly.

As for the simulation study, the accuracy of the voxel with the greatest temperature rise is highest for the analytical solution (Fig. 9), with the numerical and linear methods generally over- and underestimating the temperature rise, respectively. This is again reflected in the FWHM of the profiles as shown in Fig. S2(a). Although no “true” Q is available in this case, the linear method is generally estimating wider, and the numerical method narrower, beam widths than the analytical method.

As previously stated, being able to rapidly obtain *in vivo* SAR estimates in a clinical setting with high accuracy and

FIG. 10. (a)–(d) Phantom data showing two orthogonal views (X – Y plane and X – Z plane, respectively) of temperature maps for truth and the three methods being compared, as determined from MRTI data with applied FUS powers of 6 W, 9 W, 19 W, and 40 W, respectively. The X – Y planes have been zoomed in to better show details. [Color figure can be viewed at wileyonlinelibrary.com]

precision would be very valuable for treatment planning, monitoring, and control purposes. The presented numerical method demonstrates a step in this direction in terms of short reconstruction times. However, as seen in both the simulation and phantom studies the temporal backward propagation (deconvolution) of the Green's function greatly amplifies any noise in the input temperature maps when estimating Q , greatly reducing its accuracy. This happens already at fairly low noise levels, and can become a challenge if the user is to use the Q or SAR itself. However, if the Q is used in the PBTE the resulting temperature maps are accurate. Future studies will investigate adding temporal^{21,22} and spatial²³ smoothness constraints to the processing pipeline to denoise the estimated Q and/or the input temperatures.

5. CONCLUSIONS

The overall accuracy of the numerical inverse Green's function method makes it a promising new method for noninvasive SAR estimations. The significant gains in processing time over other methods, however, make it especially valuable in the clinical setting. With a 100-fold decrease in reconstruction time, this fast algorithm can go a long way in making thermal modeling clinically accepted, and further studies will focus on accounting for the noise amplification defect of the method.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose with regard to the work presented in this manuscript.

APPENDIX

The solution to Eq. (12) is obtained by first removing the offset temperature and then taking the spatial Fourier transform $\hat{T}_0(\vec{v}, t) = \int \int \int T_0(\vec{x}, t) e^{-i\vec{v} \cdot \vec{x}} d\vec{x}$ giving:

$$\frac{\partial \hat{T}_0}{\partial t} = -\left(\kappa v^2 \hat{T}_0 + \frac{w}{\rho} \hat{T}_0\right) \quad (\text{A.1})$$

This can be solved:

$$\frac{\partial \hat{T}_0}{\hat{T}_0} = -\left(\kappa v^2 + \frac{w}{\rho}\right) dt \quad (\text{A.2})$$

$$\hat{T}_0(\vec{v}, t) = \hat{T}_0(\vec{v}, 0) e^{-(\kappa v^2 + \frac{w}{\rho})t} \quad (\text{A.3})$$

The initial condition is obtained from:

$$\hat{T}_0(\vec{v}, 0) = \int \int \int f(\vec{x}) e^{-i\vec{v} \cdot \vec{x}} d\vec{x} \quad (\text{A.4})$$

So that the final solution is just the inverse Fourier transform of Eq. (A.3):

$$\begin{aligned} T_0(\vec{x}, t) &= \int \int \int f(\vec{x}') d\vec{x}' \\ &\int \int \int e^{-(\kappa v^2 + \frac{w}{\rho})t} e^{i\vec{v} \cdot (\vec{x} - \vec{x}')} \frac{d\vec{v}}{2\pi} \\ &= \int \int \int f(\vec{x}') \frac{1}{(4\pi\kappa t)^{3/2}} e^{-\left(\frac{(\vec{x} - \vec{x}')^2}{4\kappa t} + \frac{w}{\rho}t\right)} d\vec{x}' \end{aligned} \quad (\text{A.5})$$

which is just Eq. (14), if we let

$$K(\vec{x}, t) = \frac{1}{(4\pi\kappa t)^{3/2}} e^{-\left(\frac{|\vec{x}|^2}{4\kappa t} + \frac{w}{\rho}t\right)}. \quad (\text{A.6})$$

Note that Eq. (A.6) is equivalent to Eq. (15), which is the heat kernel. The solution to Eq. (13) can be found using a similar method.

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REFERENCES

1. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. *J Appl Physiol.* 1948;1:93–122.
2. Roemer RB, Fletcher AM, Cetas TC. Obtaining local SAR and blood perfusion data from temperature measurements: steady state and transient techniques compared. *Int J Radiat Oncol Biol Phys.* 1985;11:1539–1550.
3. Cheng H-LM, Plewes DB. Tissue thermal conductivity by magnetic resonance thermometry and focused ultrasound heating. *J Magn Reson Imaging.* 2002;16:598–609.
4. Cornelis F, Grenier N, Moonen CT, Quesson B. In vivo characterization of tissue thermal properties of the kidney during local hyperthermia induced by MR-guided high-intensity focused ultrasound. *NMR Biomed.* 2011;24:799–806.
5. Dillon CR, Vyas U, Payne A, Christensen DA, Roemer RB. An analytical solution for improved HIFU SAR estimation. *Phys Med Biol.* 2012;57:4527–4544.
6. Zhang J, Fischer J, Warner L, Oto A, Hor PH, Muthupillai R. Noninvasive, in vivo determination of uterine fibroid thermal conductivity in MRI-guided high intensity focused ultrasound therapy. *J Magn Reson Imaging.* 2015;41:1654–1661.
7. Dillon CR, Borasi G, Payne A. Analytical estimation of ultrasound properties, thermal diffusivity, and perfusion using magnetic resonance-guided focused ultrasound temperature data. *Phys Med Biol.* 2016;61:923–936.
8. Johnson SLSL, Dillon C, Odéen H, Parker D, Christensen D, Payne A. Development and validation of a MRgHIFU non-invasive tissue acoustic property estimation technique. *Int J Hyperth.* 2016;32:723–734.
9. Dillon CR, Todd N, Payne A, Parker DL, Christensen DA, Roemer RB. Effects of MRTI sampling characteristics on estimation of HIFU SAR and tissue thermal diffusivity. *Phys Med Biol.* 2013;58:7291–7307.
10. Shi YC, Parker DL, Dillon CR. Sensitivity of tissue properties derived from MRgFUS temperature data to input errors and data inclusion criteria: ex vivo study in porcine muscle. *Phys Med Biol.* 2016;61:N373–N385.

11. Kress R, Roemer R. A comparative analysis of thermal blood perfusion measurement techniques. *J Biomech Eng.* 1987;109:218.
12. Parker KJ. Effects of heat conduction and sample size on ultrasonic absorption measurements. *J Acoust Soc Am.* 1985;77:719–725.
13. Gao B, Langer S, Corry PM. Application of the time-dependent Green's function and Fourier transforms to the solution of the bioheat equation. *Int J Hyperth.* 1995;11:267–285.
14. U Vyas, DA Christensen. Ultrasound beam propagation using the hybrid angular spectrum method. In: *Proc. IEEE Eng. Med. Biol. Soc. (Vancouver, BC)*; 2008:2526–2529.
15. Ishihara Y, Calderon A, Watanabe H, Okamoto K, Suzuki Y, Kuroda K. A precise and fast temperature mapping using water proton chemical shift. *Magn Reson Med.* 1995;34:814–823.
16. De Poorter J, De Wagter C, De Deene Y, Thomsen C, Ståhlberg F, Achten E. Noninvasive MRI thermometry with the proton resonance frequency (PRF) method: in vivo results in human muscle. *Magn Reson Med.* 1995;33:74–81.
17. Tissue properties database - IT²IS Foundation. <https://www.itis.ethz.ch/virtual-population/tissue-properties/database/>, (n.d.).
18. Farrer AI, Odéen H, de Bever J, et al. Characterization and evaluation of tissue-mimicking gelatin phantoms for use with MRgFUS. *J Ther Ultrasound.* 2015;3:9.
19. Du YP, Parker DL, Davis WL, Cao G. Reduction of partial-volume artifacts with zero-filled interpolation in three-dimensional MR angiography. *J Magn Reson Imaging.* 1994;4:733–741.
20. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys.* 1984;10:787–800.
21. Adluru G, Awate SP, Tasdizen T, Whitaker RT, Dibella EVR. Temporally constrained reconstruction of dynamic cardiac perfusion MRI. *Magn Reson Med.* 2007;57:1027–1036.
22. Todd N, Adluru G, Payne A, DiBella EVR, Parker D. Temporally constrained reconstruction applied to MRI temperature data. *Magn Reson Med.* 2009;62:406–419.
23. Adluru G, Whitaker RT, Dibella EVR. Spatio-temporal constrained reconstruction of sparse dynamic contrast enhanced radial MRI data. In *IEEE Int. Symp. Biomed. Imaging*; 2007:109–112.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1. FWHM of Q_{rel} (a–c, top row) and dT (d–f, bottom row) for simulated data. The three columns show X (frequency encoding), Y (phase encoding), and Z (slice encoding), respectively. Note that for noise levels higher than 0.4°C the Q estimates from the numerical method proved to be too noisy to provide meaningful measures of the FWHM as can be seen, for example, in Fig. 4(c).

Fig. S2. FWHM of Q_{rel} (a–c, top row) and dT (d–f, bottom row) for phantom data. The three columns show X (frequency encoding), Y (phase encoding), and Z (slice encoding), respectively.

Table S1. Temperature RMSE for simulation experiments as a function of number of dynamic, and for three different spatial resolutions.