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Model Predictive Filtering MR Thermometry: effects of model inaccuracies, k-space reduction factor, and temperature increase rate

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Abstract

Purpose—Evaluate effects of model parameter inaccuracies (thermal conductivity, k , and ultrasound power deposition density, Q), k-space reduction factor (R), and rate of temperature increase ($\dot{T}$) in a thermal model-based reconstruction for MR-thermometry during focused-ultrasound heating.

Methods—Simulations and *ex-vivo* experiments were performed to investigate the accuracy of the thermal model and the model predictive filtering (MPF) algorithm for varying R and $\dot{T}$, and their sensitivity to errors in k and Q . *Ex-vivo* data was acquired with a segmented EPI pulse sequence to achieve large field-of-view (192x162x96mm) 4D temperature maps with high spatio-temporal resolution (1.5x1.5x2.0mm, 1.7s).

Results—In the simulations, 50% errors in k and Q resulted in maximum temperature root mean square errors (RMSE) of 6°C for model only and 3°C for MPF. Using recently developed methods, estimates of k and Q were accurate to within 3%. The RMSE between MPF and true temperature increased with R and $\dot{T}$. In the *ex-vivo* study the RMSE remained below 0.7°C for R ranging from 4–12 and $\dot{T}$ of 0.28–0.75°C/s.

Conclusion—Errors in MPF temperatures occur due to errors in k and Q . These MPF temperature errors increase with increase in R and $\dot{T}$, but are smaller than those obtained using the thermal model alone.

Keywords

MR Thermometry; PRF; HIFU; MPF; MRTI

Introduction

Magnetic resonance (MR) imaging is commonly used for monitoring thermal therapies such as high intensity focused ultrasound (HIFU) (1–5). It has gained popularity because of its

excellent soft tissue contrast and ability to accurately and non-invasively measure temperature change in a variety of tissues. Of the many MR parameters that are sensitive to temperature changes and have been used for MR temperature imaging (MRTI) (6–10), the gold standard is the proton resonance frequency (PRF) shift method (11,12). It relies on temperature dependent shifts in the water proton resonance frequency, and temperature maps are calculated by scaling the phase difference between consecutively acquired phase images.

One general challenge in MRTI is achieving accurate and precise temperature measurements with adequate spatial and temporal resolution over a sufficiently large field-of-view (FOV). For HIFU high spatio-temporal resolution is needed to accurately measure the focal zone heating and avoid temperature-averaging effects (both spatially and temporally), and large FOV is needed to monitor inadvertent near- and far-field tissue heating (13,14).

In MRTI, increased data acquisition speed, which can be traded for higher spatial resolution and/or larger FOV (usually more slices), has been achieved through steady state free precession (15,16), single-shot echo planar imaging (EPI) (17–20) and segmented-EPI (17,21–25) pulse sequences. As in MRI in general, k-space subsampling in combination with dedicated reconstruction methods are also widely used for faster imaging. Parallel reconstruction methods utilize the different sensitivities of multiple receiver coils to reconstruct subsampled k-space measurements (26–31). Recently, reconstruction of subsampled MRTI data with various iterative, compressed-sensing-like approaches have shown promising results (25,32–35). Such iterative approaches lead to long reconstruction times that hinder real-time availability of the temperature maps. A third approach for reconstructing temperature maps from subsampled data is utilizing a thermal model such as the Pennes bioheat transfer equation (PBTE) (36) to estimate missing data in k-space (37) or in image space (18,38,39). These methods are non-iterative and inherently better suited for real-time reconstruction. In general, temperature measurement accuracy in model-based approaches will depend on the accuracy of the model parameters.

The purpose of the present study was to investigate the effect of k-space reduction factor (R), rate of temperature increase ($\dot{T}$ - total temperature rise divided by total heating time), and model parameter inaccuracies (in ultrasound (US) power deposition density, Q , and in thermal conductivity, k) on a previously described model-based MRTI reconstruction algorithm, called model predictive filtering (MPF) (37). Simulation and *ex-vivo* porcine muscle studies using HIFU tissue heating were performed to assess the accuracy and robustness of the thermal model and the MPF algorithm. The methods were evaluated by calculating the root-mean-square-error (RMSE) of the temperature maps and by investigating what volume of tissue reached different levels of thermal dose.

Methods

Model predictive filtering

A full description of the MPF algorithm is given in the original paper (37), and only a brief description as background is given here. The first time frame (n) needs to be fully sampled so an artifact free complex image can be reconstructed. All subsequent time frames can be

subsampled with arbitrary subsampling factor and sampling scheme. To reconstruct time frame $(n+1)$ a thermal model (see below) is used to forward predict temperature map T_n to T_{n+1} and then convert it into a phase map using the PRF equation:

$$\phi_{n+1} = \phi_n + \gamma B_0 \alpha T E (T_{n+1} - T_n) \quad (1)$$

(ϕ_n =phase at time frame n , γ =gyromagnetic ratio, B_0 =magnetic field strength, α =PRF coefficient assumed to be -0.01 ppm/ $^{\circ}\text{C}$, TE =echo time). The phase map is combined with the magnitude image from time frame (n) , creating a complex image that is transformed into k-space using fast Fourier transform (FFT). In k-space the data acquired for time frame $(n+1)$ replaces corresponding predicted data before transforming back into image space and finally calculating an updated temperature map for time frame $(n+1)$.

As a thermal model the MPF algorithm uses PBTE:

$$\rho C_t \frac{\partial T}{\partial t} = k \nabla^2 T - W C_b (T - T_{blood}) + Q \quad (2)$$

(ρ =tissue density [kg/m^3], C_t/C_b =specific heat of tissue/blood [$\text{J}/\text{kg}/^{\circ}\text{C}$], T/T_{blood} =tissue/arterial blood temperature [$^{\circ}\text{C}$], k =thermal conductivity [$\text{W}/\text{m}/^{\circ}\text{C}$], W =Pennes perfusion parameter [$\text{kg}/\text{m}^3/\text{s}$], Q =power deposition density [W/m^3]), although any thermal model can theoretically be used. Since only *ex-vivo* experiments were performed $W=0$ was used throughout this work.

The original MPF work utilized 2D and 3D GRE MR pulse sequences and the methods of Cheng and Plewes (40) and Roemer *et al.* (41) to estimate k and Q . In this work we used recently developed and improved methods by Dillon *et al.* (42,43) to estimate k and Q by fitting a 2D radial Gaussian analytical solution to a pre-treatment low-power heating. A segmented-EPI pulse sequence was also used for faster data acquisition.

Simulation studies

Two sets of simulations were performed (1. *Model-only* and 2. *MPF*, both performed with and without determining model parameters using the methods of Dillon *et al.* (42,43)) to assess the effect of R , $\tilde{T}$, and model parameter inaccuracies on reconstructed temperature maps. All simulations used 3D Q -patterns modeled from a 256-element phased array US transducer (Imasonic, Besançon, France) with $2 \times 2 \times 8$ mm focal spot full-width-half-max and 0.5 mm isotropic voxels, assuming speed of sound 1540 m/s, and attenuation 0.054 Np/cm/MHz using the hybrid angular spectrum method (44). The Q -pattern, together with literature values for ρ (1000 kg/m^3) (45), C_t (2760 $\text{J}/\text{kg}/^{\circ}\text{C}$) (46), and k (0.40 $\text{W}/\text{m}/^{\circ}\text{C}$) (43), were used in PBTE to create 3D temperature maps. All simulations mimicked the *ex-vivo* experiments described below as closely as possible in terms of MR- and US-parameters used and were performed with three k-space reduction factors ($R=4, 6$, and 12) using the same subsampling scheme as for the *ex-vivo* experiments (see Supporting Figure S1 and below), three US heating durations (21, 42, and 63s), and two US powers (low/high resulting in $9/18^{\circ}\text{C}$ temperature increase). The high-power sonications for the three durations resulted in

$\dot{T}$ of 0.86, 0.43, and 0.29 °C/s. The purpose and methods (see Appendix A for detailed descriptions) of the simulations were:

1a) Model-only accuracy (MOacc)—To assess how $\dot{T}$ and errors in model parameters affect temperature predictions from the thermal model, errors in k and Q magnitude (from –50% to +50%) were introduced in simulated high-power sonications and temperatures were compared to truth.

1b) Model-only accuracy with parameter estimation (MOacc-param)— k and Q were determined from a simulated low-power sonication and then used in PBTE to predict high-power model only temperatures (by linearly scaling Q). The simulation was repeated 25 times for each of three sonication durations for a total of 75 repetitions, each with a different noise realization (zero mean Gaussian noise with standard deviation corresponding to the *ex-vivo* experiment) for the low-power sonication.

2a) MPF accuracy (MPFacc)—To assess how R , $\dot{T}$, and errors in model parameters affect temperature reconstructions using the MPF algorithm, a temporal sequence of subsampled k-spaces obtained with known (true) k and Q values were reconstructed with erroneous k and Q values (from –50% to +50%) using the MPF algorithm. The simulation was repeated for all three values of R and all three sonication durations.

2b) MPF accuracy with parameter estimation (MPFacc-param)—To assess the errors that occur in the MPF reconstruction when using model parameters determined from low-power sonications, k and Q were first determined from simulated noisy low-power sonications and then used in combination with noisy and subsampled k-space data obtained during simulated high-power sonications (by linearly scaling Q) to predict temperatures. The simulation was repeated 25 times for each of three sonication durations and three values of R for a total of 225 repetitions, each with different noise realizations for both low-power sonication and subsampled k-space.

For all simulations, temperatures obtained with the erroneous or estimated k and Q values are compared against truth obtained using known (true) values. Two different metrics were used to evaluate temperature accuracy. To determine local focal spot error the mean and STD of the peak temperature voxel were plotted as a function of time, and the RMSE of this voxel was calculated. As a more global error, the RMSE was calculated over all voxels that experienced significant temperature increase, here defined as >30% of the peak temperature truth voxel.

Ex-vivo HIFU experiments

All imaging was performed on a 3T MRI scanner (TIM Trio, Siemens Medical Solutions, Erlangen, Germany), and all HIFU heating was performed using an MR-compatible phased array US transducer (256 elements, 1 MHz frequency, 13 cm radius of curvature, 2x2x8 mm focal spot FWHM, Imasonic, Besançon, France, and Image Guided Therapy, Pessac, France). Two in-house built 2-channel receive-only RF-coils (47) were used for signal

detection. All data processing was performed using Matlab (R2013a, MathWorks, Natick, MA).

Experiments were performed on three separate samples of porcine muscle. For each sample, five sets of HIFU experiments were performed, where each set consisted of three sonications:

- #1** Small FOV low-power sonication to determine k and Q ;
- #2** Small FOV high-power sonication to determine a fully sampled estimate of truth; and
- #3** Large FOV high-power sonication that was sampled with a k-space sampling order designed to allow retrospective subsampling (see next paragraph and Supporting Figure S1) with $R=4, 6$, and 12 for reconstruction with the MPF algorithm.

For **#1** and **#2** above, each k-space was fully sampled, i.e. no subsampling was performed for these datasets. The 15 sonications in each of the three tissue samples were performed at 14/28 W (low/high-power, respectively) for 21 s in the first sample, 14/28 W for 42 s in the second sample, and 12/24 W for 63 s in the third sample. The goal was to perform low-power sonications with temperature increases of 8–10 °C for model parameter determination (**#1** above), and high-power sonications with temperature increases of 16–20 °C to determine truth (**#2** above) and for MPF reconstructions (**#3** above). The starting temperature of the samples was approximately 20 °C so limiting temperature increase to 16–20 °C ensured minimal thermal dose accumulation and allowed repeatable sonications within each sample. A 10-minute cooling period was applied between each sonication. Except for the number of slices and the slab thickness, the same MR parameters were used in all experiments: TR/TE=36/11 ms, readout bandwidth (BW)=752 Hz/pixel, echotrain length (ETL)=9, voxel size=1.5x1.5x2.0 mm³, matrix=128x108x(12/48), FOV=192x161x(24/96 mm), where 12 slices (24 mm) were used for the small FOV, and 48 slices (96 mm) were used for the large FOV (Supporting Table S1). The acquisition time was 5.2 s for the small FOV and 20.8 s for the large FOV (before subsampling). For $R=6$ and 12 the acquisition time per time frame was less than 5.2 s, so only time frames coinciding with truth time frames were used for plotting and error calculations. The flip angles used, which gave the maximum signal-to-noise-ratio for each tissue sample, were 35°, 25°, and 25°, respectively. Fat saturation by a frequency specific off-resonance RF-pulse was applied in all sonications (48). All data was zero-filled interpolated (ZFI) to 0.5 mm isotropic voxel spacing to mitigate partial volume effects and ensure accurate tissue properties determination (13,49).

The 3D segmented-EPI pulse sequence used throughout this study samples a set of k_y phase encodes for a k_z slice encode with the first echo train. The same set of k_y phase encodes is then sampled for remaining k_z slice encodes, before changing to the next set of k_y phase encodes and repeating them for all k_z , and so on until k-space is fully sampled. This sampling pattern enables retrospective down-sampling with arbitrary R without discarding any data, by dividing each fully sampled 3D k-space into multiple subsampled 3D k-spaces (Supporting Figure S1).

For each of the 15 sets of sonications the methods of Dillon (42,43) and the low-power sonication (#1 above) were used to estimate k and Q . The magnitude of Q was then linearly scaled to correspond to the high-power sonications, and *model-only* and *MPF* reconstructions were performed. Both reconstructions were evaluated against the fully sampled truth (#2 above). For *model-only* the estimated k and (scaled) Q were used in the thermal model (equation 2) - these *ex-vivo* results correspond to simulation 1b) “*MOacc-param*”. For *MPF* the estimated parameters were used together with the subsampled k-space data from the large FOV high-power sonications (#3 above) in the MPF algorithm. These *ex-vivo* results correspond to simulation 2b) “*MPFacc-param*”.

The same accuracy metrics used in the simulation study were used for the *ex-vivo* experiments. In addition MPF was also compared to reconstructing the subsampled data with a simple sliding window (SW) reconstruction, and a previously described compressed-sensing-like temporally constrained reconstruction (TCR) method (25,50). For all three reconstruction methods, the 15 high-power large FOV datasets (#3 above) were reconstructed with $R=4$, 6, and 12, corresponding to acquisition times of 5.2 s, 3.5 s, and 1.7 s. To further compare the relative performance of the three reconstruction methods, the RMSE of all voxels with temperature increase between 30–60%, 60–90%, and >90% of the hottest truth voxel were calculated and compared. The method of Sapareto and Dewey (51) was used to calculate the thermal dose cumulative equivalent minutes at 43 degrees (CEM43) for the three reconstruction methods. Tissue volumes that reached levels of 30, 100, and 240 CEM43 were compared to corresponding volume obtained using the fully sampled truth. To make meaningful dose volume comparisons and avoid effects due to different end temperatures (Table 1), the dose calculations were made assuming that an end temperature of 58 °C was reached in all cases.

One-way analysis of variance (ANOVA) tests, with follow-up multiple comparison of means tests using Bonferroni adjustments, with a level of significance $\alpha=0.05$ were performed to investigate if the different reconstruction methods resulted in significantly different RMSE and thermal dose values.

The temperature STD was investigated by calculating the mean of the STD through time of 40x40x20 voxels in an un-heated region of each porcine sample. This was done for all three durations for the fully sampled truth as well as for all sonication durations and R s for all three reconstruction methods.

To investigate the possibility of using a tabular lookup value for k , all 15 large FOV high-power datasets were further reconstructed with the MPF algorithm using the average value of k from the 15 low-power sonications in the three different porcine samples. A multiple comparison of means ANOVA test ($\alpha=0.05$) was also performed to investigate statistically significant differences.

Results

Figure 1 shows the RMSE of all voxels receiving significant heating for the “*MOacc*”- (a–c) and “*MPFacc*”-simulations (d–i). Arrows in b) and e) indicate that errors in k/Q of

−9%/+9% result in 1 °C RMSE (black contour) for “*MOacc*”, whereas for “*MPFacc*” substantially larger errors of −17%/+21% result in 1 °C RMSE.

Mean and STD of the hottest voxel vs. time for simulated (mean±STD of 25 sonications) and *ex-vivo* (mean±STD of 5 sonications) “*MOacc-param*”-experiments, for all sonication durations, are shown in Figure 2. All simulations underestimate the temperature increase, whereas for the *ex-vivo* data both over- and underestimations can be observed. For the simulations the RMSE of the hottest voxel was $0.28\pm0.01^{\circ}\text{C}$, $0.32\pm0.02^{\circ}\text{C}$, and $0.33\pm0.02^{\circ}\text{C}$ for the three durations, and corresponding values for the *ex-vivo* experiment were $0.46\pm0.11^{\circ}\text{C}$, $0.63\pm0.16^{\circ}\text{C}$, and $0.64\pm0.23^{\circ}\text{C}$.

In figures 3 and 4 mean and STD of the temperature increase of the hottest voxel vs. time for simulated and *ex-vivo* “*MPFacc-param*”-experiments are shown. For the simulation studies (Figure 3) all sonication durations and *R* can be seen to perform similarly, whereas larger differences are observed for *ex-vivo* experiments (Figure 4). The *ex-vivo* MPF reconstructions are compared to SW and TCR reconstructions, as well as to fully sampled truth. In general MPF performs better than TCR, which in turn performs better than SW. The differences are most noticeable for higher values of *R* (rightmost column), and close to sharp temporal gradients, i.e. when the ultrasound is turned on/off.

The global RMSEs for the simulation and *ex-vivo* data in Figures 2–4 are shown in Figure 5 as mean and standard error of the mean (SEM). For both simulated and *ex-vivo* MPF data (Figure 5b) the RMSE decreases for slower heating rates as well as for lower *R*s, and this is also the case for *ex-vivo* TCR and SW data. In Figures 6a)–c) the mean and SEM of the RMSE of all voxels with temperature increase between 30–60%, between 60–90%, and >90% of the hottest truth voxel, respectively, are shown for the *ex-vivo* data. In agreement with Figures 4–5 it can again be seen that MPF always performs better than SW, is always similar or better than TCR, and the improvements are much more significant for the hottest voxels. Asterisks in figures 5 and 6 indicate that the RMSE is statistically significantly different as investigated with the multiple comparison of means ANOVA test.

As shown in Figure 7, SW is significantly less accurate than MPF and TCR in terms of dosed tissue volume, with worse accuracy for faster heating rates and higher dose levels (i.e. larger errors for 240 than for 30 CEM43). Overall MPF is most accurate and dosed volumes are within 5% for all *R* and $\dot{T}$ of 240 CEM43, within 8% for 100 CEM43, and within 11% for 30 CEM43. The difference in accuracy between MPF and TCR is smaller in terms of dose than in temperature RMSE, and MPF is only significantly more accurate in 4 of the combinations of *R* and $\dot{T}$ compared.

Figure 8 shows three orthogonal views of the spatial error of the focal spot for the hottest time frame for the three reconstruction methods and truth for one of the 42 s and *R*=12 *ex-vivo* sonications, and in Supporting Figure S2 corresponding temperature maps are shown. Both Figures indicate that the MPF data agrees best with truth, although with a slight temperature overestimation at the peak of the focal zone rather than an underestimation, which is the case for TCR and SW.

The maximum temperature increase and $\dot{T}$ for all experiments are summarized in table 1.

Both simulations and *ex-vivo* experiments provided estimates of k and Q for comparison with true or previously published values. From the 300 simulated low-power sonications k and Q were overestimated compared to true values by $3\% \pm 0.9\%$ and $1\% \pm 2.5\%$, respectively. k estimated from the 15 *ex-vivo* low-power sonications in the 3 tissue samples was $0.41 \pm 0.03 \text{ W/m}^\circ\text{C}$ (individual values shown in Supporting Table S2). For comparison, the value $0.40 \text{ W/m}^\circ\text{C}$ for porcine muscle was obtained with standard invasive methods (43).

The effect of the range of measured values of k on the RMSE for the *ex-vivo* experiment was very small. The largest difference in global RMSE between reconstructing the 15 large FOV high-power datasets with the individual values of k (Supporting Table S2), and the average value of 0.41, was 0.02°C (data not shown). The ANOVA tests further showed no statistically significant differences, suggesting that a tabular value for k could have been used without significant loss of measurement accuracy.

The mean and STD of the temperature STD through time of an un-heated region in each porcine sample are shown in Supporting Table S3. All three reconstruction methods can be seen to experience lower STDs than the fully sampled data, with MPF being slightly lower than TCR, which in turn is lower than SW.

Reconstruction time for one time frame of a zero-filled 3D volume in a non-optimized Matlab implementation of the MPF algorithm on a standard laptop (2.5GHz Intel Core i7 processor and 8GB RAM, MacBook Pro, Apple, Cupertino, CA) was 1.13 s, i.e. faster than the shortest acquisition time (1.7s for $R=12$) in the present study.

Discussion and conclusion

This paper has investigated the performance of a previously described thermal model-based reconstruction method for MR thermometry data, in terms of effect of errors in model parameters, k-space reduction factor, and rate of temperature increase. Simulations and HIFU experiments in *ex-vivo* porcine muscle show that MPF is less sensitive to errors in model parameters than the thermal model alone, and that increased accuracy is achieved for lower k-space reduction factors and lower rates of temperature increase. Utilizing a 3D segmented EPI pulse sequence and k-space subsampling for increased data acquisition speed, and recently described and improved methods for model parameter determination, MPF enables accurate ($\text{RMSE} < 0.7^\circ\text{C}$) and real-time reconstructions ($\sim 1\text{s}$) of high-resolution ($1.5 \times 1.5 \times 2.0 \text{ mm}$), large FOV ($192 \times 162 \times 96 \text{ mm}$) 3D MRTI. Results also suggest that tabular values for k can be used without loss in measurement accuracy.

Simulation studies (Figure 1) show that both the thermal model and MPF are more robust to errors in model parameters if both k and Q are either over- or underestimated (in the simulation studies both parameters were slightly overestimated), in which case their effects counteract each other minimizing the errors. As can be expected, substantially reduced sensitivity to errors in model parameters is gained if subsampled k-space data is incorporated in the reconstruction algorithm as in MPF. The errors in k and Q that result in a given RMSE in the “MPFacc”-simulations are approximately double those in the “MOacc”-simulations. This is highlighted by the considerably larger red/black contours in

Figures 1d)–i) than in 1a)–c). The slope of the contours (i.e. the contours are closer to being horizontal than vertical) also suggests that the MPF reconstruction is more sensitive to relative errors in Q than in k . The “MPFacc”-simulations further show that 1) for a given R , better accuracy is achieved for lower $\dot{T}$, and 2) for a given sonication duration, better accuracy is to be expected for lower values of R .

The “MPFacc”-simulations and *ex-vivo* “MPFacc-param”-data both show increased accuracy for lower $\dot{T}$ and R , and so do TCR and SW reconstructions of the *ex-vivo* data. Slower heating results in smaller changes occurring from time frame to time frame, which simplifies model prediction for MPF and minimizes temporal smoothing-effects for TCR and SW. Although higher values of R utilize the acquired k-space data in the reconstruction algorithm closer in time to where it was actually acquired, errors increase in MPF because the erroneous model values carry more weight. The cause for the error increase for TCR and SW requires more investigation.

The *ex-vivo* MPF data (Figures 4–6) further show that MPF can accurately ($\text{RMSE} < 0.7^\circ\text{C}$) monitor sonications with $R=4\text{--}12$ and $\dot{T}=0.28\text{--}0.75^\circ\text{C/s}$, and that MPF generally performs better than TCR and SW. For areas experiencing lower temperature increases (Figure 6a) there is no statistically significant difference between MPF and TCR for any of the R and $\dot{T}$ values investigated. For these areas SW also performs as well as MPF and TCR for low values of R and $\dot{T}$, suggesting that for low to moderate R and $\dot{T}$ these off-focus areas can be reconstructed with simple reconstruction methods without loss in measurement accuracy. For regions experiencing higher temperature increase (Figures 6b–c), the RMSE for SW is significantly larger than for MPF and TCR for all cases, highlighting that, for these areas, more advanced reconstruction methods are really needed. For these higher temperatures, it is also clear that MPF is significantly more accurate than TCR in most cases, especially for low values of $\dot{T}$ and for high R . The higher accuracy and smaller errors over the focal spot for MPF is also evident in the spatial temperature and error distributions (Figure 8 and Supporting Figure S2).

In Supporting Figure S2 all three reconstruction methods can further be seen to experience less background (i.e. off-focal) temperature variation compared to fully sampled truth, in agreement with the STD through time data (Supporting Table S3). For MPF all predicted data is inherently noise-less which reduces the STD through time. In TCR the temporal constraint tends to smooth out variations in time, and for SW the same k-space lines are used in multiple consecutive time frames, which also results in lower STD through time.

Larger temperature increases than the $16\text{--}19^\circ\text{C}$ reached in this study can be achieved by increasing the sonication duration or by using higher power. Increasing the sonication duration will have a small effect on $\dot{T}$, and it can be assumed that it will not affect the temperature measurement accuracy. Using a higher power, which would minimize treatment time, will lead to higher $\dot{T}$ and hence decrease accuracy as discussed above. We note that higher temperatures can also lead to lower signal magnitude over the focal spot region, due to T_1 increase with temperature (6). Although a decreased signal might introduce a problem for the MPF algorithm, no such problems were observed in the current study. This may become an issue for tissues with already long T_1 relaxation times and grant further studies.

The thermal dose evaluation shows that MPF temperatures can also accurately predict treated volume (dose > 240 CEM43), being within 5% of the true volume for all cases of R and $\dot{T}$ (Figure 7c). The fractional differences in calculated dose between MPF and TCR are smaller than the corresponding fractional difference in temperature RMSE. As was the case for temperature RMSE, SW temperatures can be used to estimate dosed volume without loss in accuracy for slow heatings, but performs significantly worse for higher $\dot{T}$.

The simulation results indicate that accurate estimates for k and Q can be achieved with the methods used throughout this work (42,43), with the 300 simulated low-power sonications resulting in slightly overestimated values (103% for k , and 101% for Q). For the *ex-vivo* experiments, the mean value of k determined from the 15 low-power datasets (0.41 W/m²/°C) agrees well with previously published values for porcine tissue obtained with invasive measurements using a thermal properties analyzer. The spread in the value of k between the three different pieces of porcine muscle, and its effect on the temperature RMSE, further indicate that a tabular lookup value for k can possibly be used without decreasing the accuracy of the MPF reconstructions. There is no direct way to assess the accuracy of the determined Q in the *ex-vivo* experiments. However, the fact that both k (compared to gold standard invasive method) and the reconstructed temperature maps (compared to fully sampled truth) were accurate gives strong evidence that Q , just as in the simulation study, was accurately determined as well.

One of the main advantages of model-based reconstruction approaches (like MPF) compared to iterative reconstruction approaches (like TCR) is the decreased computational burden, allowing real-time reconstruction. The reconstruction time of 1.13 s per 3D volume presented here is faster than the shortest acquisition time ($t_{acq}=1.7$ s for $R=12$). This and the fact that the code has not yet been optimized for fast and parallel reconstruction, suggests that real-time availability of large FOV 3D temperature maps is achievable with MPF. If multiple receive coils are used, these can be reconstructed in parallel without an increase in reconstruction time.

Both local and global RMSEs for simulated and *ex-vivo* “*MOacc-param*”-studies (Figures 2 and 5a) show, contrary to corresponding MPF results, larger errors for slower heating rates. Since these are model-only reconstructions, any errors caused by erroneous k and Q estimates will propagate in time, resulting in the larger errors observed for longer heating durations. All three simulated predictions (Figures 2a and 5a) are underestimated, in agreement with the larger observed overestimation in k (103%) than in Q (101%). From corresponding *ex-vivo* data (Figures 2b and 5a) the 21 s sonications agree well with truth, while the 42 and 63 s sonications demonstrate over- and underestimations, respectively. While nothing can be deduced about Q in this case, the observed over-/underestimations are consistent with observed under-/overestimations of k (0.39 and 0.43 W/m²/°C, respectively, Supporting Table S2), compared to the previously reported value for porcine muscle.

Since the tissue used throughout this study was relatively homogenous, it was assumed that ρ , C , and k were spatially constant, and only Q was estimated in 3D. For inhomogeneous tissue, it can be hypothesized that Q can still be accurately determined in 3D since it is based on 3D temperatures. If inhomogeneous tissues can be accurately segmented, tabular values

for ρ , C , and k for the different tissue types can be used, but further studies are needed to investigate the effect on MPF accuracy. More inhomogeneous tissues will also lead to susceptibility artifacts, but these are likely to be small as long as significant temperature increase does not occur near tissue-air interfaces. Since only non-perfused tissue was investigated W was set to zero in all reconstructions. For *in-vivo* applications the effects of blood perfusion will need to be taken into account, and can be determined with previously described methods (41,52–56). Lastly, MPF in the presence of motion was described in the original MPF paper (37), but was beyond the scope of this manuscript. *In-vivo* motion might be a concern depending on the organ targeted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jolesz, FA.; Hynynen, KH. MRI-Guided Focused Ultrasound Surgery. New York: Informa Healthcare; 2008.
2. Hokland S, Pedersen M, Salomir R, Quesson B, Stødkilde-Jørgensen H, Moonen C. MRI-guided focused ultrasound: methodology and applications. *IEEE Trans. Med Imaging*. 2006; 25:723–731.
3. Medel R, Monteith SJ, Elias WJ, Eames M, Snell J, Sheehan JP, Wintermark M, Jolesz FA, Kassell NF. Magnetic resonance-guided focused ultrasound surgery: Part 2: A review of current and future applications. *Neurosurgery*. 2012; 71:755–63. [PubMed: 22791029]
4. Schlesinger D, Benedict S, Diederich C, Gedroyc W, Klivanov A, Lerner J. MR-guided focused ultrasound surgery, present and future. *Med Phys*. 2013; 40:080901. [PubMed: 23927296]
5. Ellis S, Rieke V, Kohi M, Westphalen AC. Clinical applications for magnetic resonance guided high intensity focused ultrasound (MRgHIFU): present and future. *J Med Imaging Radiat Oncol*. 2013; 57:391–9. [PubMed: 23870333]
6. Parker DL. Applications of NMR imaging in hyperthermia: an evaluation of the potential for localized tissue heating and noninvasive temperature monitoring. *IEEE Trans Biomed Eng*. 1984; 31:161–7. [PubMed: 6724602]
7. Graham SJ, Bronskill MJ, Henkelman RM. Time and temperature dependence of MR parameters during thermal coagulation of ex vivo rabbit muscle. *Magn Reson Med*. 1998; 39:198–203. [PubMed: 9469702]
8. Chen J, Daniel BL, Butts Pauly K. Investigation of proton density for measuring tissue temperature. *J Magn Reson imaging*. 2006; 23:430–4. [PubMed: 16463298]
9. Le Bihan D, Delannoy J, Levin R. Temperature mapping with MR imaging of molecular diffusion: Application to hyperthermia. *Radiology*. 1989; 171:853–857. [PubMed: 2717764]
10. Graham SJ, Stanisz GJ, Kecojovic A, Bronskill MJ, Henkelman RM. Analysis of changes in MR properties of tissues after heat treatment. *Magn Reson Med*. 1999; 42:1061–71. [PubMed: 10571927]
11. 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. [PubMed: 7891538]

12. 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; 34:814–23. [PubMed: 8598808]
13. Todd N, Vyas U, de Bever J, Payne A, Parker DL. The effects of spatial sampling choices on MR temperature measurements. *Magn Reson Med*. 2011; 65:515–21. [PubMed: 20882671]
14. Odéen H, de Bever J, Almquist S, Farrer A, Todd N, Payne A, Snell JW, Christensen DA, Parker DL. Treatment envelope evaluation in transcranial magnetic resonance-guided focused ultrasound utilizing 3D MR thermometry. *J Ther Ultrasound*. 2014; 2:19. [PubMed: 25343028]
15. Scheffler K. Fast frequency mapping with balanced SSFP: theory and application to proton-resonance frequency shift thermometry. *Magn Reson Med*. 2004; 51:1205–11. [PubMed: 15170841]
16. Paliwal V, El-Sharkawy A-M, Du X, Yang X, Atalar E. SSFP-based MR thermometry. *Magn Reson Med*. 2004; 52:704–8. [PubMed: 15389940]
17. Kickhefel A, Roland J, Weiss C, Schick F. Accuracy of real-time MR temperature mapping in the brain: a comparison of fast sequences. *Phys medica*. 2010; 26:192–201.
18. Denis de Senneville B, Roujol E, Hey S, Moonen C, Ries M. Extended Kalman filtering for continuous volumetric MR-temperature imaging. *IEEE Trans Med Imaging*. 2013; 32:711–8. [PubMed: 23268383]
19. Roujol S, Ries M, Quesson B, Moonen C, Denis de Senneville B. Real-time MR-thermometry and dosimetry for interventional guidance on abdominal organs. *Magn Reson Med*. 2010; 63:1080–7. [PubMed: 20373409]
20. Holbrook AB, Santos JM, Kaye E, Rieke V, Butts Pauly K. Real-time MR thermometry for monitoring HIFU ablations of the liver. *Magn Reson Med*. 2010; 63:365–73. [PubMed: 19950255]
21. Cernicanu A, Lepetit-Coiffe M, Roland J, Becker CD, Terraz S. Validation of fast MR thermometry at 1. T with gradient-echo echo planar imaging sequences: phantom and clinical feasibility studies. *NMR Biomed*. 2008; 21:849–858. [PubMed: 18574794]
22. Weidensteiner C, Quesson B, Caire-Gana B, Kerioui N, Rullier A, Trillaud H, Moonen CTW. Real-time MR temperature mapping of rabbit liver in vivo during thermal ablation. *Magn Reson Med*. 2003; 50:322–30. [PubMed: 12876709]
23. De Zwart JA, Vimeux FC, Delalande C, Canioni P, Moonen CTW. Fast lipid-suppressed MR temperature mapping with echo-shifted gradient-echo imaging and spectral-spatial excitation. *Magn Reson Med*. 1999; 42:53–9. [PubMed: 10398950]
24. Madore B, Panych LP, Mei C-S, Yuan J, Chu R. Multipathway sequences for MR thermometry. *Magn Reson Med*. 2011; 66:658–68. [PubMed: 21394774]
25. Todd N, Adluru G, Payne A, DiBella EVR, Parker D. Temporally constrained reconstruction applied to MRI temperature data. *Magn Reson Med*. 2009; 62:406–19. [PubMed: 19353648]
26. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med*. 1999; 42:952–62. [PubMed: 10542355]
27. Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magn Reson Med*. 2002; 47:1202–10. [PubMed: 12111967]
28. Guo JY, Kholmovski EG, Zhang L, Jeong E-K, Parker DL. k-space inherited parallel acquisition (KIPA): application on dynamic magnetic resonance imaging thermometry. *Magn Reson Imaging*. 2006; 24:903–15. [PubMed: 16916708]
29. Mei CS, Panych LP, Yuan J, McDannold NJ, Treat LH, Jing Y, Madore B. Combining two-dimensional spatially selective RF excitation, parallel imaging, and UNFOLD for accelerated MR thermometry imaging. *Magn Reson Med*. 2011; 66:112–22. [PubMed: 21337421]
30. Weidensteiner C, Kerioui N, Quesson B, Denis de Senneville B, Trillaud H, Moonen CTW. Stability of real-time MR temperature mapping in healthy and diseased human liver. *J Magn Reson imaging*. 2004; 19:438–46. [PubMed: 15065167]
31. Bankson JA, Stafford RJ, Hazle JD. Partially parallel imaging with phase-sensitive data: Increased temporal resolution for magnetic resonance temperature imaging. *Magn Reson Med*. 2005; 53:658–65. [PubMed: 15723414]

32. Marx, M.; Butts Pauly, K. Use of Compressed Sensing for Acceleration of Volumetric MR Thermometry. 9th International Interventional MRI Symposium; Boston. 2012. p. 110
33. Cao Z, Oh S, Otazo R, Sica CT, Griswold MA, Collins CM. Complex difference constrained compressed sensing reconstruction for accelerated PRF thermometry with application to MRI-induced RF heating. *Magn Reson Med*. 2014 Epub ahead of print. 10.1002/mrm.25255
34. Zhao F, Noll DC, Nielsen J, Fessler JA. Separate magnitude and phase regularization via compressed sensing. *IEEE Trans Med Imaging*. 2012; 31:1713–23. [PubMed: 22552571]
35. Gaur P, Grissom WA. Accelerated MRI Thermometry by Direct Estimation of Temperature from Undersampled k-Space Data. *Magn Reson Med*. 2014 Epub ahead of print. 10.1002/mrm.25327
36. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. *J Appl Physiol*. 1948; 1:93–122. [PubMed: 18887578]
37. Todd N, Payne A, Parker DL. Model predictive filtering for improved temporal resolution in MRI temperature imaging. *Magn Reson Med*. 2010; 63:1269–79. [PubMed: 20432298]
38. Fuentes D, Yung J, Hazle JD, Weinberg JS, Stafford RJ. Kalman filtered MR temperature imaging for laser induced thermal therapies. *IEEE Trans Med Imaging*. 2012; 31:984–94. [PubMed: 22203706]
39. Roujol S, Denis de Senneville B, Hey S, Moonen C, Ries M. Robust adaptive extended Kalman filtering for real time MR-thermometry guided HIFU interventions. *IEEE Trans Med Imaging*. 2012; 31:533–42. [PubMed: 21997254]
40. Cheng H-LM, Plewes DB. Tissue thermal conductivity by magnetic resonance thermometry and focused ultrasound heating. *J Magn Reson imaging*. 2002; 16:598–609. [PubMed: 12412038]
41. 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; 11:1539–50. [PubMed: 4019278]
42. Dillon CR, Vyas U, Payne A, Christensen DA, Roemer RB. An analytical solution for improved HIFU SAR estimation. *Phys Med Biol*. 2012; 57:4527–44. [PubMed: 22722656]
43. Dillon CR, Payne A, Christensen DA, Roemer RB. The accuracy and precision of two non-invasive, magnetic resonance-guided focused ultrasound-based thermal diffusivity estimation methods. *Int J Hyperth*. 2014; 30:362–71.
44. Vyas U, Christensen D. Ultrasound beam simulations in inhomogeneous tissue geometries using the hybrid angular spectrum method. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2012; 59:1093–100. [PubMed: 22711405]
45. Chato JC, Lee RC. The Future of Biothermal Engineering. *Ann N Y Acad Sci*. 1998:1–20. [PubMed: 9917802]
46. The Engineering Toolbox. [Accessed on 22/04/14] Food and Foodstuff - Specific Heats. http://www.engineeringtoolbox.com/specific-heat-capacity-food-d_295.html
47. Hayes CE, Mathis CM, Yuan C. Surface coil phased arrays for high-resolution imaging of the carotid arteries. *J Magn Reson Imaging*. 1996; 6:109–112. [PubMed: 8851414]
48. Haase A, Frahm J, Hänicke W, Matthaei D. 1H NMR chemical shift selective (CHESS) imaging. *Phys Med Biol*. 1985; 30:341–4. [PubMed: 4001160]
49. 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; 58:7291–307. [PubMed: 24077026]
50. Todd N, Vyas U, de Bever J, Payne A, Parker DL. Reconstruction of fully three-dimensional high spatial and temporal resolution MR temperature maps for retrospective applications. *Magn Reson Med*. 2012; 67:724–30. [PubMed: 21702066]
51. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys*. 1984; 10:787–800. [PubMed: 6547421]
52. Craciunescu OI, Das SK, McCauley RL, MacFall JR, Samulski TV. 3D numerical reconstruction of the hyperthermia induced temperature distribution in human sarcomas using DE-MRI measured tissue perfusion: validation against non-invasive MR temperature measurements. *Int J Hyperth*. 2001; 17:221–239.

53. Huttunen JM, Huttunen T, Malinen M, Kaipio JP. Determination of heterogeneous thermal parameters using ultrasound induced heating and MR thermal mapping. *Phys Med Biol.* 2006; 51:1011–32. [PubMed: 16467593]
54. Dragonu I, Lourençode Oliveira P, Laurent C, Mougenot C, Grenier N, Moonen CTW, Quesson B. Non-invasive determination of tissue thermal parameters from high intensity focused ultrasound treatment monitored by volumetric MRI thermometry. *NMR Biomed.* 2009; 22:843–51. [PubMed: 19562728]
55. 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. [PubMed: 21834004]
56. Dillon, C.; Roemer, R.; Parker, D.; Payne, A. A novel method for quantifying perfusion-induced energy losses in magnetic resonance-guided focused ultrasound. Society for Thermal Medicine; Minneapolis: 2014. p. Wed.32

Figure 1.

Global RMSE of all voxels with temperature increases greater than 30% of the maximum true temperature. a)–c) “*MOacc*”-simulations for 21s, 42s, and 63s, d)–i) “*MPFacc*”-simulations with $R=4$ for 21s, 42s, and 63s, and for 42s with $R=4$, 6, and 12. Errors in Q (vertical axis) and k (horizontal axis) vary from -50% to $+50\%$. Red/Black contours indicates RMSE of 0.5/1.0°C. Arrows in b) and e) show that k/Q errors of $-9\%/+9\%$ and $-17\%/+21\%$ result in RMSE of 1°C for “*MOacc*” and “*MPFacc*”, respectively. Please note the difference in scale between a)–c) and d)–i).

Figure 2. Temperature rise of hottest voxel vs. time for a) simulated and b) *ex-vivo* “MOacc-param”, both for 21s, 42s, and 63s heatings. The RMSE shows a slight increase for longer heating durations (i.e. slower heatings) in both simulations and *ex-vivo* experiments.

Figure 3.

Mean and STD temperature rise of the hottest voxel vs. time for “*MPFacc-param*”-simulations. a) for $R=4$, b) for $R=6$, and c) for $R=12$, all three for 21s, 42s, and 63s heating duration.

Figure 4.

Mean and STD temperature rise of the hottest voxel vs. time for *ex-vivo* “MPFacc-param” experiments. a)–c) 21s heating duration, d)–f) 42s heating duration, and g)–i) 63s heating duration, all for $R=4, 6$, and 12 . MPF is compared to truth, SW and TCR. Note that for $R=6$ and 12 , which have higher temporal resolution than the truth, only time frames that coincide with the truth are plotted.

Figure 5.

Mean and SEM of RMSE of all voxels with significant temperature rise for a) “*MOacc-param*” for simulated and *ex-vivo* data, and b) “*MPFacc-param*” for simulated and *ex-vivo* data, the latter reconstructed with MPF, TCR and SW. For the *ex-vivo* data in b), the asterisks (*) indicate that the RMSE is significantly different than the RMSE for the other reconstruction methods as evaluated by the multiple comparison of means ANOVA test.

Figure 6. Mean and SEM for RMSE of all voxels with temperature rise a) between 30% and 60%, b) between 60% and 90%, and c) above 90% of the hottest truth voxel. Asterisks indicate that the RMSE is statistically significantly different (as tested by the multiple comparison of means ANOVA test) than the RMSE for the other reconstruction methods.

Figure 7.

Mean and SEM of tissue volume reaching a) 30, b) 100, and c) 240 CEM43 compared to true volume. Asterisks indicate that the dosed volume is statistically significantly different (as tested by the ANOVA test) than the dosed volume for the other reconstruction methods.

Figure 8.

Three orthogonal views of spatial error for the hottest time frame for a) MPF, b) TCR, and c) SW, all for one of the 42s *ex-vivo* runs with $R=12$. Subfigure d) shows the truth run for comparison.

Table 1

Maximum temperature increase and $\dot{T}$ achieved for low- and high-power simulation and ex-vivo heatings for all three durations.

		Simulation Low-power	Simulation High-power	Ex-vivo Low-power	Ex-vivo High-power
21 s	Max T (°C)	9	18	8.3±0.62	15.8±0.98
	$\dot{T}$(°C/s)	0.43	0.86	0.40	0.75
42 s	Max T (°C)	9	18	10.4±0.30	19.3±0.37
	$\dot{T}$(°C/s)	0.21	0.43	0.25	0.46
63 s	Max T (°C)	9	18	9.4±0.72	17.3±0.89
	$\dot{T}$(°C/s)	0.14	0.29	0.15	0.28