MRI-GUided LASer THERMAL ABLATION: MODEL AND PARAMETER ESTIMATES RELATING MR THERMOMETRY IMAGES TO CELL DEATH

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ABSTRACT

Solid tumors and other pathologies can be treated using laser thermal ablation under interventional magnetic resonance imaging (iMRI) guidance. We developed a model to predict cell death from MR thermometry measurements and applied it to \textit{in vivo} rabbit brain data. We aligned post-ablation MR lesion images to gradient echo images, from which temperature is derived, using a mutual information registration method. We used the outer boundary of the hyperintense rim in the post-ablation MR lesion image as the boundary for cell death, as verified from histology. Model parameters were simultaneously estimated using an iterative optimization algorithm applied to every interesting voxel in over 185 images from multiple experiments having various temperature histories. The model gave a voxel sensitivity and specificity of 86.9\% and 98.8\%, respectively. Mislabeled voxels typically were within one voxel of the segmented necrotic boundary. This is good evidence that iMRI temperature maps can be used with our model to predict therapeutic regions in real-time.

1. INTRODUCTION

Solid tumors and other pathologies can be treated using laser thermal ablation under interventional magnetic resonance imaging (iMRI) guidance. Magnetic resonance imaging (MRI) has several advantages including, excellent soft tissue discrimination, sensitivity to temperature, and ability to image at any angle. To monitor an ablation procedure, MRI can continuously acquire temperature images during heating, and structural images during and after heating. We are investigating the ability to monitor treatment using MR thermometry measurements. A model relating temperature history to cell death could be used to predict the therapeutic region in real time during the heating process, thereby allowing one to treat the pathology and spare adjoining critical tissues.

The use of MR thermometry measurements and a cell death model to predict therapeutic regions has advantages. First, although post-ablation MR lesion images accurately predict the region of cell death \cite{1}, these can only be obtained several minutes after the ablation, possibly after undesirable damage is done. Because MR temperature images could provide real-time feedback during the ablation, one can cease application at the appropriate moment. Second, post-ablation MR structural images may not distinguish the edema that surrounds the thermal lesion from tumors, hemorrhage, or prior inflammation. Thermometry measurements might be less ambiguous in these cases. Third, the MR temperature measurements using the proton resonance frequency (PRF) method are accurate and, except for fat, independent of tissue type \cite{2}. Furthermore, a model of tissue damage is needed in any quantitative pre-procedural planning strategy \cite{3}.

There are various potential tissue damage models to use with MR temperature data. Previous reports have used a critical temperature model that assumes the cell death is not observable below the critical temperature and occurs extremely rapidly and completely above the critical temperature \cite{2,4,5}. This model neglects the temperature history. Others used a mathematical model of the temperature-time relationship for tissue damage. These models usually consisted of either a generalized Arrhenius function \cite{6} or a linear approximation of the Arrhenius function near 43\textdegree C with fixed model parameters \cite{2,4,5,7}. However, the empirically-derived values for these Arrhenius-based models can vary for different tissues, temperature ranges, and heating durations \cite{8}.

There are various methods to compare model results to the tissue response. In previous reports, analysis was often done using geometric measurements without alignment of MR temperature images with images of the necrotic region as determined by histology or post-ablation MR data \cite{6,7}. For example, Hazle et al. measured diameters of necrotic regions in macroscopic tissue images and calculated diameters of cell death regions predicted by a tissue damage model. In 15 lesions, mean diameters agreed within 2 mm. Obviously, a voxel-by-voxel assessment would be desirable, especially for nonsymmetrical lesions.

We developed a new tissue damage model and applied it on a voxel-by-voxel basis to temperature-time histories as obtained from multiple MR thermometry measurements. Our method includes image registration, image filtering, and iterative parameter estimation techniques. We first describe the model and then apply it to the image data from rabbit brain.

2. METHODS

2.1 Model

We used a mathematical model that predicts the region of cell death. Below, we describe the thermal damage model, fitting procedure, and pertinent mathematics. The complete method and subsequent analysis were implemented using MATLAB.
Our model is based on the local time-varying temperature. As the temperature increases during a thermal ablation, the kinetic energy of the molecules increases. This thermal agitation of molecules at high kinetic energies disrupts chemical bonds which can lead to various destructive processes including influx of Ca, rupture of cell membranes, and denature of intracellular proteins to cause cell death [9]. Our assumption is that the severity of these destructive events can increase to a threshold value that leads to cell destruction.

At elevated temperatures, we assume that a normal cell will accumulate “destruction” to a point where it will die. Extending this concept to a slightly more macroscopic view, we assume that there will be destruction (D) to tissue in a region starting in the native condition (N). The build up of destruction will depend both upon temperature and duration through a temperature dependent rate coefficient, $\beta(T(t))$, as shown below.

$$N(t) \rightarrow D(t)$$

where the temperature, $T(t)$, is a function of $t$, time. The corresponding differential equation is:

$$-\frac{dN(t)}{dt} = \beta(T(t)) N(t),$$

and the analytical solution is:

$$N(\tau) = N(0) e^{-\int_0^\tau \beta(T(t))dt}$$

The accumulated “destruction” of tissue, $\Omega(\tau)$, is defined as the percent of tissue destroyed:

$$\Omega(\tau) = \frac{D(\tau)}{N(0)} = 1 - e^{-\int_0^\tau \beta(T(t))dt}$$

where: $N(\tau) = N(0) - D(\tau)$

The temperature response of a heated voxel during ablation will typically show the temperature increase to a maximum, remain at the maximum for some duration, and then decrease to the basal temperature when heating stops. Above a critical temperature, $T_c$, the destruction of tissue can occur. When the temperature falls below $T_c$, destruction stops. In addition, since the rate of tissue destruction is expected to increase with temperature, $\beta$ is expected to be a monotonically increasing function with respect to temperature. We used the following mathematical expression for $\beta$, which consisted of three parameters ($A, N, T_c$).

$$\beta[T(t)] = \begin{cases} 0, & T(t) < T_c \\ A(T(t) - T_c)^N, & T(t) \geq T_c \end{cases}$$

The severity of the accumulated destruction increases to a critical threshold value, $\Omega_C$, that leads to cell death. The model outputs ($M$) are the final cell state:

$$M = \begin{cases} 0(\text{normal}), & \Omega(\tau) < \Omega_c \\ 1(\text{dead}), & \Omega(\tau) \geq \Omega_c \end{cases}$$

This threshold is based on an all or nothing tissue response observed in histology minutes post-ablation that shows a sharp transition between dead and adjacent normal cells [1]. Thus, the final model includes four parameters: $A, N, T_c, \Omega_c$. We will refer to this set of parameters as $\theta$.

### 2.2 Parameter estimation

We want to fit the model to a segmented cell death binary image ($S$), as verified from histology. Model outputs, $M(\theta)$, are estimated for each voxel in a sequence of temperature images, $T(t)$, to create an estimated cell death binary image. From the temperature images, we computed the time integral for equation 4 numerically using trapezoidal integration. We determine the difference between the estimated and segmented cell death images on voxel-by-voxel basis. The sum of the absolute differences from $N$ voxels across $R$ ablations is a scalar measure of fit quality for the entire ablation data set, as shown by the objective function $f(\theta)$.

$$f(\theta) = \sum_{j=1}^R \sum_{i=1}^N |M_{ij}(\theta) - S_{ij}|$$

Iterative minimization of Equation 8 yields the parameter estimates that best fit the model to segmented data. Many optimization algorithms are suitable for a nonlinear search of parameter space. Typically the choice of algorithm depends on the tradeoff between the number of objective function evaluations and resistance to local minima. Because our objective function is computationally inexpensive, such that each evaluation requires only a fraction of a second on a Pentium 4 class computer, we used the Nelder-Mead simplex method [10] for its robustness and resistance to discontinuities in parameter space despite a large number of expected iterations.

### 2.3 Laser ablation and MR imaging

We used a 0.5 T open MRI system to guide a laser fiber (5 mm long conical tip, 0.2 mm diameter) between two parallel rice noodle fiducials inserted into each in vivo rabbit brain, and continuously acquire gradient echo (GE) MR phase images (TR/TE = 77.2/38.9 msec; FOV = 16 x 16 cm; matrix = 256 x 128; slice thickness = 3.0 mm, flip angle = 30°, imaging time = 10 seconds, voxels = 0.6 x 1.2 x 3.0 mm) before, during, and after heating, and obtain T2-weighted spin-echo MR images (TR/TE = 4000 msec; matrix = 512 x 256; FOV = 16 x 16 cm; slice thickness = 2 mm; number of excitations = 4; voxels = 0.3 x 0.6 x 2.0 mm) at four hours post-ablation. All MR images were acquired in the same plane and parallel to the laser fiber and rice noodle fiducials. A fiber-optic temperature sensor was inserted 4 mm lateral to the laser fiber to measure baseline temperature. Ablation occurred by heating the tissue with a 2 W laser power source (1064 nm wavelength). A reference phantom, separated from each animal by 2 cm, was used to correct any phase drift during imaging. For calibration of the PRF shift thermal coefficient, we performed ablations on six in vivo brains. To correlate the modeled tissue damage to the tissue response, we
created a thermal lesion in four brains, with heating durations of 30, 120, 180, 570 seconds. To provide immediate assessment of the heating, MR temperature maps were created in near real-time by subtracting baseline phase maps and reference phantom phase from remaining phase maps.

2.3 Image Processing

Since GE MR phase images can be noisy on a low-field system, we applied temporal filtering to the temperature maps. We removed transient noise spikes with a temporal grayscale morphological filter. Each voxel was temporally filtered across the entire sequence of temperature maps. We created movies of the temperature map sequences to visually confirm the removal of the transient noise spikes. This filtering process was implemented in a conservative manner to produce an enhanced image sequence with reduced noise and no blurring of temperature distributions.

We used a previously developed 2D rigid body registration method to align the post-ablation T2-weighted MR lesion image with the sequence of GE MR images used for temperature mapping. First, we manually registered the T2-weighted image to a few minutes post-ablation GE image by aligning the skull bone, internal anatomical features, and fiducials placed near the lesion. Second, we applied the voxel-based mutual information registration method that was previously shown to achieve sub-voxel accuracy for brain registration [11].

To compare the model predicted regions of cell death with the tissue response, we created a binary cell death image. For each lesion, we manually segmented the outer boundary of the hyperintense rim in the four hours post-ablation T2-weighted MR lesion image. The correlation of the outer boundary of the hyperintense rim in the T2-weighted MR image with the region of necrosis assayed from registered histology, was previously validated [1]. After segmentation, each voxel value along and inside the segmented boundary was set to one, else it was zero. The set of segmented binary cell death images from all experiments was used for subsequent model fitting and error estimation.

3. RESULTS

In Figure 1, we show a typical in vivo MR temperature map registered to a post-ablation T2-weighted MR lesion image. The plane of both images was oriented parallel to the laser fiber and the two rice noodle fiducials used for registration. The unfiltered MR temperature map shows the spatial temperature distribution with exceptionally low noise in the unheated peripheral region. The T2-weighted MR lesion image reveals a central isointense core surrounded by a distinct circular hyperintense rim. Based on previous studies, the outer boundary of the hyperintense rim in the T2-weighted MR lesion image corresponds to boundary of necrosis as seen in registered histology images on the order of one MR voxel [1].

After model parameters were optimized simultaneously for all ablation experiments, we determined that the model coupled with in vivo MR temperature maps can predict the region of necrosis, with any mislabeled voxels typically lying within one voxel of the segmented necrotic boundary. Results for a typical experiment are shown in Figure 2. The model performance across all ablations showed a sensitivity and specificity of 86.9% and 98.8%, respectively. The estimated values for the model parameters $A$, $N$, $T_C$, $\Omega_C$ were 0.0064, 1.01, 43.2, 0.62, respectively. For each MR temperature map, the time to solve the model equations on a Pentium 4 class computer was 16 ms for a 25 x 25 voxel region of interest.

![Figure 1. Typical MR-derived images for a rabbit brain ablation. Registered images are: temperature map (top) and T2-weighted MR post-ablation lesion image (bottom). Temperature map shows spatial distribution of temperature during laser heating with approximately circular symmetry. In T2-weighted MR image, the circular outer boundary of the lesion’s hyperintense rim, which corresponds to the necrotic boundary, is clearly visible. Two rice noodles used for registration are the dark vertical lines on each side of lesion.](image-url)
4. DISCUSSION

Our results suggest that it is possible to use in vivo MR temperature images and a thermal damage model to predict regions of cell death. Because of its simplicity, our model could be practically applied during thermal ablations. In real-time, model predicted regions of cell death could be overlaid on iMRI images or even on registered SPECT and high resolution MR tumor images acquired before treatment. Predictions could then be visually compared to a segmented pathology to give real-time feedback to the physician. Both the preprocessing time and the time to solve the equations are negligible as compared to the typical time of 10 s between MR thermometry images. The same model should be applicable to other potential temperature measuring techniques such as ultrasound.

We can compare our model and data analysis technique to previously reported ones. Arrhenius-based models using parameters from other experiments not surprisingly did not always work [5]. A time-temperature product model did not work [4]. Maximum temperature typically does much better [4,5]. We use a differential equation model that considers the temperature time history. In principal this model will be able to predict a wider range of temperature time histories. The latter point is being investigated. Our analysis method uses all interesting voxels unlike previous reports which only analyzed voxel-by-voxel basis addresses these limitations and should enable a more accurate prediction of the necrotic region.

We conclude that our tissue damage model with a sequence of MR temperature maps can be used to accurately predict the tissue response. Results show that for in vivo rabbit brain, the estimated region of necrosis closely corresponds to the segmented region of cell death. This is good evidence that MR temperature maps can be used with our thermal damage model to predict the therapeutic region in real-time.

5. ACKNOWLEDGEMENTS

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6. REFERENCES