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A Model Evaluation Study for Treatment Planning of Laser Induced Thermal Therapy

S. Fahrenholtz^{1,2}, T. Moon³, M. Franco³, D. Medina³, S. Danish⁴, A. Gowda⁵, A. Shetty⁵, F. Maier¹, J. D. Hazle^{1,2}, R. J. Stafford^{1,2}, T. Warburton³, and D. Fuentes^{1,2,*}

¹The University of Texas M.D. Anderson Cancer Center, Department of Imaging Physics, Houston, TX 77030, USA

²The University of Texas at Houston, Graduate School of Biomedical Sciences, Houston, TX 77030, USA

³CAAM, Rice University, Houston, TX 77005, USA

⁴Robert Wood Johnson, New Brunswick, NJ 08901, USA

⁵BioTex, Inc., Houston, TX 77054, USA

Abstract

A cross validation analysis evaluating computer model prediction accuracy for *a priori* planning magnetic resonance-guided laser induced thermal therapy (MRgLITT) procedures in treating focal diseased brain tissue is presented. Two mathematical models are considered. (1) A spectral element discretization of the transient Pennes bioheat transfer equation is implemented to predict the laser induced heating in perfused tissue. (2) A closed-form algorithm for predicting the steady state heat transfer from a linear superposition of analytic point source heating functions is also considered. Prediction accuracy is retrospectively evaluated via leave-one-out cross validation (LOOCV). Modeling predictions are quantitatively evaluated in terms of a Dice similarity coefficient (DSC) between the simulated thermal dose and thermal dose information contained within $N = 22$ MR thermometry datasets. During LOOCV analysis, the transient model's DSC mean and median is 0.7323 and 0.8001, respectively, with 15 of 22 DSC values exceeding the success criterion of DSC = 0.7. The steady state model's DSC mean and median is 0.6431 and 0.6770, respectively, with 10 of 22 passing. A one-sample, one-sided Wilcoxon signed rank test indicates that the transient FEM model achieves the prediction success criteria, DSC = 0.7, at a statistically significant level.

Keywords

Bioheat Transfer; Laser Induced Thermal Therapy; MR Temperature Imaging; GPU Computing

*Corresponding Author: dtfuentes@mdanderson.org.

1 Introduction

Approximately 211,000 patients present each year in the US with brain tumors. Of these, 38,000 are benign primary tumors, 23,000 malignant primary tumors, and 150,000 are metastatic, originating largely from lung, breast, and melanoma [1–5]. The average life expectancy for patients with primary and metastatic malignancies in the brain, from time of diagnosis until death, is approximately 12–16 months. Five year survival is among the lowest of all cancers. Current treatment options include conventional surgery, stereotactic radiosurgery (SRS), or chemotherapy. Surgical resection may be preferred for patients presenting with a single, solitary lesion, or lesions greater than 2.5 cm – 3.0 cm in which the size or location of the tumor causes neurological symptoms such as seizures, headaches, cognitive or motor deficits, that can be resolved by reducing the volume of the disease. SRS, such as Gamma Knife[®], is typically performed on patients with multiple tumors, tumors under 2.5 cm in diameter, and deep seated tumors [6]. An additional target in brain is epileptogenic foci for patients with medically refractory epilepsy, where MRgLITT is being considered for the surgical armamentarium for those patients [7, 8]. Unfortunately, patients with malignant recurrences who have reached maximum radiation dose limitations and complications with surgical resection create a group of patients with no remaining conventional treatment options; meanwhile patients with medically refractory epilepsy have limited interventions available. Magnetic resonance-guided laser induced thermal therapy (MRgLITT) presents an alternative, minimally invasive thermal ablation technique for these groups of patients and has been safely and successfully applied to each [9–15].

Under MR guidance, the laser applicator is carefully navigated through critical structures and placed directly into the diseased tissue to induce ablative heating and destroy the tissue. Real-time thermometry of the treatment volume during laser heating provides a mechanism by which it is possible to deliver these therapies in both a safe and effective manner [16–19] as well as estimate the extent of tissue damage [20–22]. However, the heating induced by the laser is not constrained exclusively to tumor tissue and nearby tissue damage is possible. For these procedures to progress to standard of care, *a priori* determination of the optimal placement of the laser catheter(s) is crucial for achieving a more conformal delivery of therapy over the target volume with minimal comorbidity of intervening or adjacent tissue. Surgical workflows in which the operating room and MRI suite are separate [7, 23] exaggerate the advantages of a predictive model.

This manuscript focuses on the development of a practical methodology for evaluating computer model predictions for *a priori* planning the procedure given N datasets from previous procedures. Evaluation focuses on prediction accuracy for guiding applicator placement. Retrospective analysis of MR thermometry data acquired during previous procedures is essential to train or calibrate the computer model parameters. The machine learning and statistics community have a rich history in applying various algorithmic and physics-based data models to reach conclusions from a given dataset [24, 25]. Here we assume that a Pennes bioheat transfer model [26] provides representative predictions of the physical process underlying the heating observed within the MR thermometry data. This physics-based approach provides a theoretically sound and concise methodology to

statistically summarize the high dimensional thermometry dataset with a low dimensional model parameter subset.

Two distinct modeling approaches are pursued: (1) A GPU implementation of an unstructured hexahedral spectral element method for predicting the bioheat transfer is developed. (2) A computationally inexpensive algorithm for predicting the heat transfer from a linear superposition of analytic point source heating functions is also presented as a reference implementation. Combined with the data, the two modeling approaches presented provide an environment to critically evaluate model accuracy and selection for therapy planning of MRgLITT. Both approaches build intuition in the prediction by repetitively training the underlying physics model to statistically match representative datasets. Predictions are critically evaluated in terms of solution efficiency and accuracy for prospective treatment planning of MRgLITT procedures. Leave-one-out cross validation (LOOCV) is used to simulate the clinical scenario in which N datasets from previous procedures are available to calibrate the computer model. LOOCV provides an objective framework to critically estimate the accuracy and confidence in predicting the outcome of the procedure for the $N + 1$ patient [27–31].

2 Methods

2.1 Thermometry Data

MR thermal monitoring from MRI guided stereotactic laser induced thermal therapy (LITT) was considered in $N = 22$ MR thermometry datasets. The datasets were vetted for motion artifacts, low signal-to-noise, and catheter induced signal voids that spuriously reduce the modeling accuracy. Each patient was treated with The Visualize Thermal Therapy System (Visualase, Inc., Houston, TX). The Visualase[®] system includes a 15 W 980 nm diode laser, a cooling pump, and a laser applicator set. The laser applicator set is disposable and consists of a 400 μm core silica fiber optic with a cylindrical diffusing tip housed within a 1.65 mm diameter saline-cooled polycarbonate cooling catheter [12,22]; see Figure 1. Applicator cooling lines and laser fiber optics are connected through a waveguide between the control room and the bore of the MR magnet. An MR compatible headholder is used to secure the patient's head. The trajectory to the targeted tumor lesion was obtained using the Brainlab navigation system (Brainlab, Westchester, IL USA). A battery-powered hand drill was used to place a threaded plastic bone anchor within the skull. The laser applicator is secured to the threaded plastic bone anchor. The Visualase[®] system imports images from a 3D MPRAGE sequence to verify applicator position within the lesion. The depth is determined by the navigation software and is input retrospectively within this study.

MR temperature imaging was performed on a 1.5 T MRI (GE Healthcare Technologies, Waukesha, WI) using a 2D gradient echo sequence [32] ($\text{FA} = 30^\circ$, $\text{FOV} = 24 \times 24 \text{ cm}^2$, matrix size = 256×128 , $\text{TR/TE} = 37.5/20 \text{ ms}$, receive-only head coil, 5 seconds per update). The imaging plane was chosen perpendicular to the axial direction of the applicator and allowed monitoring of critical structure regions. The Visualase[®] workstation communicates with the MR scanner to obtain raw DICOM imaging data during the procedure. The temperature dependent water proton resonance frequency shift is measured by calculating the complex phase-difference observed during heating. The water proton resonance

frequency chemically shifts to lower frequencies with higher temperatures (caused by rupture, stretching, bending of hydrogen bonds) [33]. The total temperature change, Δu , is proportional to the measured phase change, $\delta\phi$.

$$\Delta u = \frac{\delta\phi}{2\pi\alpha \cdot \gamma B_0 \cdot TE}$$

Here α is the temperature sensitivity coefficient, γ is the gyromagnetic ratio of water, B_0 is the static magnetic field strength, and TE is the echo time. A baseline body temperature of $u_0 = 37.0^\circ\text{C}$ is assumed to obtain absolute temperature. An Arrhenius rate process model [34] was used to evaluate the thermal dose resulting from the time-temperature history of the laser exposure.

$$\Omega(t) = \int_0^t A e^{\frac{-E_A}{Ru(\tau)}} d\tau \quad (1)$$

In this Arrhenius thermal dose model, the frequency factor, A , and the activation energy, E_A , are experimentally determined kinetic parameters. The values for A and E_A were $3.1\text{E}98\text{ s}^{-1}$ and $6.28\text{E}5\text{ (J/mol)}$, respectively, and have been used in previous studies [9,35,36]. R is the universal gas constant. The thermal dose was assumed to be lethal at doses $\omega \geq 1$ as seen in previous reports [9, 36].

Prior to treatment delivery, a low power test pulse—*e.g.*, 4 W for 30 s—is applied to verify position of the diffusion fiber optic within the catheter. The test pulse is sufficient to allow thermal visualization but not cause thermal damage. Multiple thermal imaging datasets are available per patient; only the therapeutic pulses are considered in this study. A representative laser power profile used during the therapy is shown in Figure 1. All DICOM header information was imported into an SQLite database to provide efficient queries and organize thermometry data for reproducible analysis and processing. The schema provided by the Slicer [37] DICOM module was used as template for the table structure. The object identifier (OID) of the SQL table was used to provide anonymous references to the data. The SQL functions, `group by`, `group_concat`, and `count`, were used in quality assurance of the data location, number of files, etc. Metadata needed for the analysis includes:

1. The applicator orientation and heating region of interest (ROI) are manually identified within the imaging datasets for input into the computer models discussed in Sections 2.2 and 2.3.
2. A text file containing the relevant laser power history for each imaging dataset is parsed and input into the simulation. The power history provides information on the heating and cooling time intervals during the procedure.

2.2 Simulation of Bioheat transfer within Laser Irradiated Tissue

A time dependent Pennes [26] bioheat transfer equation provides a computer model for predicting the temperature field resulting from the laser tissue interaction.

$$\partial u_t - \nabla \cdot (\alpha \nabla u) + \frac{\omega c_{\text{blood}}}{\rho c_p} (u - u_a) = \frac{1}{\rho c_p} q_{\text{laser}} \quad \text{in } U \setminus U_{\text{tip}} \quad (2)$$

$$q_{\text{laser}}(x, t) = \int_{U_{\text{tip}}} \frac{p(t) \mu_{\text{eff}}^2}{\text{Vol}(U_{\text{tip}})} \frac{\exp(-\mu_{\text{eff}} \|x - \xi\|)}{4\pi \|x - \xi\|} d\xi \quad x \in U \setminus U_{\text{tip}}$$

$$\alpha = \frac{k}{\rho c_p} \quad \mu_{\text{eff}} = \sqrt{3\mu_a \mu_{\text{tr}}} \quad \mu_{\text{tr}} = \mu_a + \mu_s(1 - g)$$

$$n \cdot (\alpha \nabla u) = 0 \quad \text{on } \partial U \quad n \cdot (\alpha \nabla u) = h(u - u_{\text{cooling}}) \quad \text{on } \partial U_{\text{tip}}$$

Here the tissue specific heat, c_p ; tissue density, ρ ; thermal conductivity, k ; perfusion, ω ; blood specific heat, c_{blood} ; and arterial blood temperature, u_a , are deterministic model parameters obtained from literature [38–40]; see Table 1. The laser source, q_{laser} , is a deterministic function of the applied power, $p(t)$; optical scattering, μ_s ; optical absorption, μ_a ; anisotropy factor, g ; and distance, $\|x - \xi\|$, from the source, U_{tip} . Active cooling of the water owing through the applicator is modeled by a Robin or mixed boundary condition in which the temperature flux at the applicator interface is proportional to the convection coefficient, h , and the temperature difference between the cooling fluid u_{cooling} and the tissue. A diagram of the Visualase[®] applicator used in this application is shown in Figure 1.

An implicit Euler time discretization is used to reduce the time-dependent bioheat equation, Equation (2), into a sequence of elliptic problems. Hexahedral Lagrange elements (polynomial order = 3) were used in the finite element discretization of the spatial domain. These elements use a tensor-product of Gauss-Lobatto-Legendre (GLL) interpolation nodes and are commonly referred to as spectral elements. A matrix-free preconditioned conjugate gradient algorithm is used to solve the linear system of equations inherent to the discretization. An overlapping additive Schwarz preconditioner is used since the local block problem on each element is well suited for the block-coupled parallelism of the wide SIMD cores on the GPU. The matrix-free approach minimizes the storage requirements and data movement of the finite element elliptic solvers. The preconditioned conjugate gradient algorithm does not explicitly demand the system matrix to be stored but only requires the evaluation of matrix-vector products, and the structure of the tensor-product hexahedral elements allow this action to be computed with $\mathcal{O}(N^4)$ operations per degree- N finite element. Avoiding assembly and storage of the stiffness matrix on the GPU allows the solver to handle discretizations with a large number of elements to compensate for the limited memory on the GPU. This algorithmic approach is shown to have high computational efficiency on the non-uniform memory architecture of modern GPUs [41].

All computations were performed on the template hexahedral mesh shown in Figure 1 (b). For each simulation, the template was registered to the observed laser location for each patient. The mesh consists of disjoint regions for the applicator and tissue. A quadrilateral mesh was extruded axially along the applicator to create the base of the hexahedral finite element mesh. The mesh for the tissue conforms to the surface of the application and extends sufficiently far to ensure that the boundary does not influence the heating. The discretization consists of $N_{dof}=844,032$ total GLL nodes. The degrees of freedom across the volume of the applicator were removed; the effect of the room-temperature cooling fluid which protects the laser fiber during heating were considered through the boundary conditions at the surface nodes. Similar to previous studies [42], multiple mesh resolutions were considered to ensure convergence of the discretized solution; a mesh resolution approximating the 1 mm pixel size near the applicator was used. Multiple time resolutions were also evaluated to ensure convergence of the time stepping scheme.

2.3 Analytic Steady State Solution

A steady state version of the Pennes bioheat equation, Equation (2), was also considered as a surrogate model for the therapy planning, in order to investigate the accuracy of a simpler, trained model. Constant coefficients are assumed. A 1D spherically symmetric radial

decomposition of the solution, $u(r) - u_a = \frac{\mathcal{R}(r)}{r}$, simplifies the analysis of the differential operator in spherical coordinates.

$$\frac{\omega c_{\text{blood}}}{\rho c_p} \frac{\mathcal{R}(r)}{r} - \frac{\alpha}{r} \frac{d^2 \mathcal{R}}{dr^2} = \frac{\mu_{\text{eff}}^2 P \exp(-\mu_{\text{eff}} r)}{\rho c_p 4\pi r}$$

$$u(r_1) = u_0 \quad \left. \frac{du}{dr} \right|_{r_2} = 0 \quad r_1 < r_2$$

From classical theory [43], the general solution is the linear combination of the homogeneous solution, u_h , and a particular solution,

$u_p = \frac{1}{r} (A \exp(-\mu_{\text{eff}} r) + B r \exp(-\mu_{\text{eff}} r))$. In this case, the particular solution was obtained from the method of undetermined coefficients for $A, B \in \mathbb{R}$.

$$u = \underbrace{C_1 \frac{\exp(\sqrt{\frac{\omega c_{\text{blood}}}{k}} r)}{r} + C_2 \frac{\exp(-\sqrt{\frac{\omega c_{\text{blood}}}{k}} r)}{r}}_{u_h} + \underbrace{\frac{\mu_{\text{eff}}^2 P \exp(-\mu_{\text{eff}} r)}{4\pi r (\omega c_{\text{blood}} - k \mu_{\text{eff}}^2)}}_{u_p} + u_a \quad (3)$$

The boundary conditions are used to determine the coefficients of the homogeneous solution. Applicator cooling is specified by the boundary condition at $r = r_1$. The domain is assumed large enough that no heat flux is observed at the far boundary $r = r_2$.

$$\begin{bmatrix} \frac{\exp\left(\sqrt{\frac{\omega c_{blood}}{k}} r_1\right)}{\frac{r_1}{r}} & \frac{\exp\left(-\sqrt{\frac{\omega c_{blood}}{k}} r_1\right)}{\frac{r_1}{r}} \\ \frac{d}{dr} \frac{\exp\left(\sqrt{\frac{\omega c_{blood}}{k}} r\right)}{r} \Big|_{r_2} & \frac{d}{dr} \frac{\exp\left(-\sqrt{\frac{\omega c_{blood}}{k}} r\right)}{r} \Big|_{r_2} \end{bmatrix} \begin{bmatrix} C_1 \\ C_2 \end{bmatrix} = \begin{bmatrix} u_0 - u_p(r_1) - u_a \\ -\frac{du_p}{dr} \Big|_{r_2} \end{bmatrix}$$

The 1D solution provides an estimate of the heating from a single point source with applicator boundary at r_1 . Mathematica 7 (Wolfram, Champaign, IL) was used to determine and verify all coefficients. Then, ccode was used to write out the kernel. Similar analytical solutions are provided in [44–46]. Heating caused by the cylindrical geometry of the diffusing tip was modeled as evenly distributed point sources, $M=10$, along the axial dimension of the applicator at positions r_{0i} .

$$u = \sum_{i=1}^M u_h(r - r_{0i}) + u_p(r - r_{0i}) \quad (4)$$

2.4 Model Calibration

For each thermometry dataset discussed in Section 2.1, an inverse problem was solved to calibrate both computer models considered to the observed heating. Previous work [47] showed that the optical parameters provide the highest sensitivity in the temperature predictions over the range of physically meaningful model parameters. Consequently, optical parameters are considered in the optimization. The analytical form of the standard diffusion approximation for the laser source term concisely represents the heating as a function of the single optical parameter, μ_{eff} . At the end of optimization for one MRTI dataset, the dataset has a corresponding optimal μ_{eff} that is constant in space and time.

The out-of-plane translation component, z , of the mesh template shown in Figure 1 was also optimized. The physics of the MR thermometry data acquisition averages the temperature over the slice thickness and the translation update is implemented to tune the registration of the computational domain to the MR thermometry data. The remaining input parameters are assumed fixed.

The DAKOTA (Sandia National Laboratories) [48] library was used to optimize μ_{eff} for the transient and steady state models. The L_2 error over space and time was used as the objective function.

$$(\mu_{calib}, z_{calib}) = \arg \min_{(\mu_{eff}, z)} \sum_{k=1}^{N_{step}} \|u(t_k) - u^{MRTI}(t_k)\|^2$$

Thermometry data is denoted u^{MRTI} . All time steps were considered for the transient analysis of the computer model presented in Section 2.2. For the steady state model presented in Section 2.3, the objective function was the L_2 norm between the model and the MRTI's maximum heating time point. A quasi-Newton optimization method,

opp_q_newton, was implemented as the optimization algorithm for both models. Gradients of the objective functions were computed using numerical finite differences. The calibration was solved as a bound constrained optimization problem. A physically feasible parameter bound on the optimization of the optical parameters, $\mu_{eff} \in [0.8, 400] \text{ m}^{-1}$, was obtained from literature [39]. During calibration, the initial value for μ_{eff} was 180 m^{-1} . The initial value was calculated via the μ_{eff} identity from Equation (2) and the μ_a , μ_s , and g values from Table 1. The slice thickness of the MR thermometry data was used to bound the optimization of the template out of plane translation.

2.5 Leave-One-Out Cross Validation

Leave-One-Out Cross Validation (LOOCV) is a method for estimating a trained, *i.e.* calibrated, model's accuracy in prediction [27–31]. Within this context, developing a 'predictive model' refers to the process by which we can confidently assign a probability to a treatment outcome, such as full tumor destruction or damage to surrounding healthy tissue. Similar to the human cognitive process, the predictive computer model is built from prior experience using MR temperature imaging data used to monitor the procedure. The datasets are used to calibrate the computer model parameters as discussed in Section 2.4. The LOOCV algorithm is executed as:

- for each thermometry dataset $i = 1, \dots, N$
 - The average value for the optical coefficient, $\bar{\mu}_{eff}^i$, is learned from the calibration results, μ_{calib}^j , on the remaining $j \neq i$ datasets.

$$\bar{\mu}_{eff}^i = \frac{1}{N-1} \sum_{j \neq i} \mu_{calib}^j$$

- Tissue damage on the i -th dataset is predicted by using the average, $\bar{\mu}_{eff}^i$, values from the $j \neq i$ cohort. The Dice similarity coefficient (DSC) provides an estimate of the agreement with Arrhenius damage measured from thermometry data.

$$DSC(\bar{\mu}_{eff}^i) = 2 \frac{A \cap B}{A + B} \quad \bar{\mu}_{eff}^i \neq \mu_{calib}^j$$

The DSC measures the area of overlap between the area enclosed by the Arrhenius damage model for the thermometry data, A , and the computer model prediction, B . The Arrhenius damage, Equation (1), is computed from the simulated temperature field of the transient analysis. The isotherms are used as the damage model for the steady state analysis. Previous work in canine brain demonstrated that the 57°C isotherm produce damage regions similar to the

Arrhenius model for the ablation regime considered in this study [49].

The trained model's predictive ability is evaluated by analyzing the distribution of DSC values from the N iterations of LOOCV. A one-sample, one-sided Wilcoxon signed rank test examines if the trained model prediction's median exceeds $DSC = 0.7$. One-sample calculations were computed using a threshold DSC value, 0.7, as the null hypothesis, H_0 .

$$H_0: DSC = 0.7 \quad H_1: DSC > 0.7$$

The value chosen is a commonly accepted value in image processing literature [49–51]; $DSC = 1$ implies complete agreement between the measure and predicted damage model, *i.e.*, the predicted and measured damages volumes completely overlap. A two-sample, paired Wilcoxon signed rank test was used to compare if the two models' prediction medians are statistically different from one another. All statistical tests and descriptive statistics were evaluated on GraphPad Prism 6.01 (GraphPad Software, La Jolla, CA).

3 Results

Representative thermometry images and calibrated computer model predictions are shown in Figure 2. The measured and predicted thermal dose is displayed. The Arrhenius damage model is shown for the transient model predictions, Equation (2), and the thermometry data. The 57 degreeCelsius isotherm damage model is shown for the steady state analysis, Equation (4). Significant variability is seen in the heating due to local patient tissue heterogeneities, tumor location, and nearby heat sinks in the brain such as large blood vessels and cerebral spinal fluid (CSF). This is reflected by the non-ellipsoidal shape of the isotherms and corresponding damage volume in the Arrhenius estimates of the damage. However, the calibrated thermal damage predictions show acceptable agreement, *i.e.* DCE .7 [51], between the measured and predicted tissue damage in multiple patients.

The calibration process applied to each thermometry dataset provides a histogram of μ_{eff} values in which the optimal agreement between the model's prediction and the MR thermometry is observed for each model. The histogram of the μ_{eff} values for both the transient and steady state model calibrations is shown in Figure 3. Literature values of the expected optical properties is provided as a reference. Extrema of the feasible set are obtained from the range of values observed in literature. Descriptive statistics of the optimized μ_{eff} values, DSC during optimization, and DSC during LOOCV for both models is provided in Table 2; meanwhile, percentiles corresponding to interesting DSC thresholds are presented in Table 3.

The overall DSC performance from both models during LOOCV analysis is provided in Figure 4. The performance is summarized by the number of datasets that pass a given DSC threshold; the plot is analogous to the Kaplan-Meier survival curve. During LOOCV, the transient model had 15 of 22 datasets pass the $DSC = 0.7$ success criterion, while the steady state model passed 10 of 22.

The two-sample, paired Wilcoxon signed rank test rejected the null hypothesis with a p -value of 0.0059. *I.e.*, the difference of the transient and steady state models' medians of DSC during LOOCV was statistically significant. The one-sample, one-sided Wilcoxon signed rank test for the transient model rejected the null hypothesis with a p -value of 0.029. *I.e.*, the transient model's median of DSC during LOOCV was 0.7 at statistically significant level. The one-sample, one-sided Wilcoxon signed rank test for the steady state model accepted the null hypothesis with a p -value of 0.0732. *I.e.*, the steady state model's median of DSC during LOOCV was not 0.7 at a statistically significant level.

4 Discussion

Given the number of available datasets, the LOOCV analysis provides a methodology to recapitulate the clinical scenario for treatment planning. Prior knowledge and experience is embodied within the thermometry data from the previous N ablations. Information from the previous ablations is extracted by calibrating a computer model to the available data. In this case, we calibrate our optical parameter to the thermometry data. Modeling goals are to ultimately utilize the calibrated model in optimizing the thermal dose delivery. The success or failure of this paradigm is related to several factors. First, there must be a sufficient quantity of retrospective datasets for the training to converge. Second, the cohort of retrospective datasets used in training must have sufficient similarity within the group and to the prediction scenarios. Third, the model must be able to describe clinically relevant ablations.

If the LOOCV analysis only includes datasets that can be optimized to have DSC 0.7, both models perform very well. This is because the calibrated μ_{eff} values have a much tighter distribution; *i.e.* datasets with an optimal DSC 0.7 had similar μ_{eff} values. Given this investigation is framed as a prediction on the $N+1$ patient, cherry-picking the successful optimizations is inappropriate. Indeed, optimization results with DSC < 0.7 are included in the LOOCV analysis as seen in the descriptive statistics, Table 2. However, it is worth realizing that successful optimizations have similar μ_{eff} values and perhaps information beyond the thermometry data would allow the calibration to be grouped into similar cohorts. *E.g.*, additional meta information on the primary disease type, tumor location, and treatment history would provide useful information in the analysis that may demonstrate clustering during the calibration and would further classify the tissue type.

The two models presented provides a canonical model selection comparison of the trade-off between the time investment in the algorithm, efficiency of the numerical implementation, and accuracy required for predicting the final endpoint of the application. The two-sided, two-sample paired Wilcoxon signed rank test indicates the predictive results' medians are significantly different and only the transient model's median DSC performance was significantly 0.7. As a quantitative reference, the forward solve mapping between model parameters, Table 1, and temperature field is considered the fundamental computational operation of this study. Total runtimes in the analysis are proportional to the total number of forward solve iterations in the optimization and LOOCV analysis. The run times for the forward solves in this study averaged 1.87E2 s and 1.12E1 s for the transient model GPU implementation and steady state CPU implementation; respectively. These numbers are

intended to provide intuition for the observed practical run times on a local CPU (Intel Xeon, 6 core, 2.4 GHz, double precision peak 57 Gops) workstation with attach GPU accelerators (NVIDIA Tesla M2070 double precision peak 515 Gops) available to this study. The finite element discretization of the governing equations requires significant expertise of the GPU computing architecture as well as detailed algorithmic understanding of both the finite element technology and matrix-vector multiply within the iterative linear system solver to maximize floating point operation throughput and minimizes memory transactions latencies. As opposed to explicitly storing and reading matrix entries from global memory, the matrix-free method recalculates the local matrix entries needed within the linear system solve. This memory access design pattern has demonstrated a 4–10× speedup over the matrix explicit methods [41,52,53]. Meanwhile, the steady state superposition analysis, Equation (4), provides treatment predictions with fewer floating point operations and would be selected under an Occam razor [54] philosophy highly preferential to simplicity. While all kernels for the present spectral element methods and preconditioned conjugate gradient method were hand coded in this manuscript, library implementations of the matrix-free iterative solver approach are also appearing [55, 56].

The finite element discretization of the governing equations, however, provides significant opportunity for further physics-based improvements including higher order model spherical harmonic expansions in the laser fluence model [57]. As seen in Figure 3, the chosen models introduce a bias in the model parameter recovery that differs from published literature values. The bias may arise from inaccuracies in the modeling assumptions, perhaps most significant being the use of optical tissue properties that are invariant in space and time. The literature has clear examples where temperature/damage dependent and spatio-temporal dependent parameters are critical to the prediction [58,59]. The use of thermometry data during only the test pulse is also expected to influence the recovered optical properties. The choice to use a single constant parameter for full time history of each MRTI dataset is motivated by the practical model training focus of this investigation. Higher order physics models of the fluence are expected to provide the highest accuracy in recovering the optical parameters during the calibration process and for characterizing the tissue properties.

The finite element discretization of the governing equations also provides a rigorous physics-based methodology to incorporate tissue heterogeneities into the treatment prediction. Calibrations of the spatially heterogeneous optical parameter field has been shown to provide highly accurate predictions [60–62]. The inclusion of spatially varied, damage dependent, and multiple parameters should be pursued in future efforts. Adjoint-based methods of computing the gradient of the objective function are necessary to efficiently optimize in the higher dimensional parameter space. Tissue heterogeneities could similarly be incorporated into the steady state superposition analysis, Equation (4), in a patient-specific ‘*ad hoc*’ manner. However, this would violate the underlying homogeneous tissue parameter assumptions which provided the mathematical structure for the concise analytical solution. A Gaussian process [63, 64] framework may be appropriate in which the model parameters recovered may be interpreted as hyperparameters for the covariance kernels. Similar to physics-based model calibration, optimization of the hyperparameters in the Gaussian process kernels offers a complementary trade-off between data fitting and

smoothing. Further, Gaussian processes allow for prior information to be used and provide a full probabilistic prediction and an estimate of the uncertainty.

Model calibration and training was limited to thermometry data in these efforts. The predictive capabilities are expected to improve with more information provided by pre-treatment MR imaging such as dynamic contrast enhanced imaging or perfusion imaging to help guide the selection of the model parameters, especially if these preoperative images can inform the optical parameters. Incorporating tissue heterogeneities into the model predictions would also require segmentations of the neuro-anatomy as a template for the regional heterogeneity. Each direction would benefit from the forethought of including these data acquisitions into the therapy protocol. For example, current brain segmentation techniques [65] require high resolution FLAIR, T2, and T1 imaging with and without contrast. The SQL database used in organizing all data was vital to the reproducibility of the analysis in these efforts; this additional information must be incorporated. Tools for communicating with the neuro-navigation software to locate the fiber would also provide further information to improve the analysis throughput and reproducibility. Passive tracking of the applicator location using fiducials placed on the fiber would additionally provide the registration information needed to align the computational domain of the mathematical model.

Conclusion

Currently, the neurosurgeon reviews anatomical MR images to plan his/her trajectory to reach the tumor with neuro-navigation software, but does not have the capability to visualize outcomes of the laser ablation using various trajectories beforehand. Fully developed and commercially implemented predictive computer models will extend this functionality to include *a priori* visualization and optimization of the potential outcomes for complex treatment scenarios (multiple applicators/trajectories) in which the laser ablation is performed near a critical structure within a heterogeneous tissue environment. This work presents a step in this direction and demonstrates the feasibility in establishing a confidence in these predictions. Consideration of other available metadata to improve prediction accuracy is a topic of on-going research.

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Declaration of Interest

At the time of this work, Visualase, Inc. and BioTex, Inc. provided the surgical device technology and services. Drs. Shetty and Gowda were employed by those companies. Since that time, Medtronic, Inc. has acquired Visualase, Inc., and employs Dr. Shetty. BioTex, Inc. employs Dr. Gowda. Dr. Danish has received educational honoraria from Medtronic, Inc.

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Figure 1.

(a) The Visualase® applicator modeled in this application and a diagram of the photon emitting diffusing tip and the cooling fluid are shown. (b) A finite element mesh conforms to the applicator and is used as the template for the calculations. (c) A representative time-temperature history profile of the thermometry data at two points within the brain tissue, ~1 mm from the applicator, is shown. The corresponding power history is also shown.

Figure 2.

Representative thermometry data and calibrated model damage predictions. (a) The magnitude of the complex valued thermometry data provides a visualization of the anatomy and is provided as a reference. The applicator trajectory is observed as a signal void in the image. The ROI displayed has a $3.75 \times 3.28 \text{ cm}^2$ field of view and is shown in (b)–(d). (b) MR thermometry at maximum heating is shown. (c) FEM model predicted Arrhenius damage is compared to Arrhenius damage based on MRTI. (d) A comparison of the steady state damage model is shown. The steady state damage model is the region enclosed by the 57°C isotherm. The color map indicates the geometrical overlap used in DSC calculations; the legend is at right (e). Respective DSC values for the FEM model (c) and steady state model (d) are $\text{DSC} = 0.8385$ and $\text{DSC} = 0.7442$.

(a)

(b)

Figure 3.

Presented here are histograms of calibration analysis from the transient FEM model (a) and steady state model (b), shown left and right; respectively. Both histograms have a bin width of 13.0 m⁻¹. The optical parameters, μ_{eff} , recovered from each thermometry dataset considered is shown. For each calibration, the bound constrained optimization was restricted to a range obtained from literature, $\mu_{eff} \in [0.8, 400]$ m⁻¹. Leave-one-out cross validation was performed using these 22 μ_{eff} values. The nominal value in brain tissue obtained from [39] is $\mu_{eff} = 180$ m⁻¹.

Figure 4.

Here, the overall predictive performance, measured by DSC, is displayed for both models.

(a) Left is the performance during optimization, and the right is during LOOCV (b). The horizontal axis displays increasing DSC thresholds; the vertical axis displays the number of datasets that pass the DSC threshold. Greater area under the curve (AUC) indicates better prediction. In the FEM LOOCV plot, there is one dataset that has a DSC = 0 and therefore does not appear on the plot.

Table 1

Constitutive data [38–40]

$\frac{W}{K [mK]}$	$\frac{kg}{\omega [m^3s]}$	$g [Unity]$	$\mu_s [cm^{-1}]$	$\mu_a [cm^{-1}]$	$\frac{kg}{\rho [m^3]}$
0.527	9.0	0.88	14000	500	1045
$c_{blood} \frac{J}{kgK}$	$c_p \frac{J}{kgK}$	W $h [K m^3]$	$u_{cooling} [^{\circ}C]$	$u_a [^{\circ}C]$	
3840	3600	100	21	37	

Table 2

Here are the descriptive statistics for μ_{eff} during optimization and DSC performance during optimization and LOOCV ($N = 22$). The transient solve of the Pennes bioheat equation using the Arrhenius damage, Equation (1), is denoted FEM. Steady state analysis using the 57°C isotherm damage model is denoted GF. Note that all DSC, skewness, and kurtosis quantities are unitless. “%-ile” refers to percentiles. *E.g.*, 25%-ile means the dataset’s DSC performance exceeds 25% of the population DSC values in ranked order.

Descriptive Statistic	FEM	GF μ_{eff} (m ⁻¹)	FEM	GF DSC opt.	FEM	GF DSC LOOCV
Minimum	67.26	138.4	0.4865	0.3421	0	0.3312
25%-ile	115.5	167.2	0.7356	0.5789	0.6709	0.5617
Median	121.6	189.6	0.8142	0.6925	0.8001	0.6770
75%-ile	146.1	212.4	0.8652	0.7259	0.8429	0.7257
Maximum	154.6	269.4	0.8972	0.8476	0.8859	0.8143
Mean	125.6	194.7	0.7824	0.6493	0.7323	0.6431
Standard Deviation	21.78	38.42	0.1091	0.1274	0.1930	0.1289
Skewness	-0.7906	0.5714	-1.432	-1.190	-2.830	-1.150
Kurtosis	1.026	-0.2562	1.609	1.142	9.919	0.6817

Table 3

Here are the percentiles that correspond to several interesting DSC thresholds. The “opt.” and “LOOCV” columns refer to the same groups of datasets described in Table 2, as well as the datasets plotted in Figure 4. The smaller the percentile value, the better the model’s performance. ‘0’ indicates all values pass at the given threshold; ‘100’ indicates no values pass.

DSC threshold (Unity)	FEM (%-ile)	GF DSC opt. (%-ile)	FEM (%-ile)	GF DSC LOOCV (%-ile)
0.4	0	8.357	5.776	7.176
0.5	2.996	13.34	6.652	14.06
0.6	11.36	27.34	12.97	27.52
0.7	15.25	57.64	30.35	58.61
0.75	30.53	83.22	41.36	85.11
0.8	44.36	95.12	49.97	96.14
0.85	67.19	100	82.06	100