Prediction of Laser Ablation in Brain: Sensitivity, Calibration, and Validation

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PREDICTION OF LASER ABLATION IN BRAIN: SENSITIVITY, CALIBRATION, AND VALIDATION

by

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PREDICTION OF LASER ABLATION IN BRAIN: SENSITIVITY, CALIBRATION, AND VALIDATION

A

DISSERTATION

Presented to the Faculty of
The University of Texas
Health Science Center at Houston
and
The University of Texas
M. D. Anderson Cancer Center
Graduate School of Biomedical Sciences
in Partial Fulfillment
of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by
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B.Sc., Kansas State University, 2009
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In the style of Johann Sebastian Bach,
Acknowledgments

I thank R. Jason Stafford, PhD, for claiming me as I vacillated though times of shameful helplessness and brilliant autonomy. I thank David Fuentes, PhD, for directing me to fruitful computational tools and skepticism, enabling eureka! moments. I thank John D. Hazle, PhD, for his leadership at MD Anderson and within the AAPM, providing a community capable of so much innovation and service. I thank Jim Bankson, PhD, for his affable yet rigorous approach to working in research. I thank Arvind Rao, PhD, for being a data scientist with whom I can communicate.

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Abstract

The surgical planning of MR-guided laser induced thermal therapy (MRgLITT) stands to benefit from predictive computational modeling. The dearth of physical model parameter data leads to modeling uncertainty. This work implements a well-accepted framework with three key steps for model-building: model-parameter sensitivity analysis, model calibration, and model validation.

The sensitivity study is via generalized polynomial chaos (gPC) paired with a transient finite element (FEM) model. Uniform probability distribution functions (PDFs) capture the plausible range of values suggested by the literature for five model parameters. The five PDFs are input separately into the FEM model to gain a probabilistic sensitivity response of the model to the input PDFs. The result demonstrates the model output variance is dominated by the three optical parameters and the two remaining parameters contribute less.

The second aim is model calibration, given the need to acquire model parameter data of greater precision sans physical measurement. The availability of a relatively large cohort of $N = 22$ clinical laser ablations of metastases gradient-based inverse problems provides inference of the optical parameter values, the most sensitive parameter as indicated by gPC, from patient MR temperature imaging (MRTI). In order to accelerate the bioheat model for iteration during parameter optimization, two simplified models are conceived: (1) a homogeneous, transient FEM model implemented on GPU and (2) a homogeneous, steady-state, analytic model implemented on GPU. After model optimization — i.e., calibration — the model validation immediately follows via leave-one-out cross-validation (LOOCV). LOOCV compares the two trained models’ predictive performances. During LOOCV, the FEM model correctly predicts 15 of 22; the steady state model correctly predicts 17 of 22. A steady state model using naive literature values correctly predicts only 10 of 22. When training on an $N = 20$ cohort tailored to only include ablations near steady state, the trained steady state model correctly predicts 19 of 20 patient datasets versus the 8 of 20 predicted by an untrained steady state model.

The conclusion is model training is an effective means of improving model performance when there is lack of accurate and precise parameter data in the literature, especially when there is little prospect of improving data quality. A key to success in this model-training paradigm is to have a training/calibration cohort that has adequate similarity to the predicted/validation cohort.
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Abbreviations

CA Cryoablation. x, 6, Glossary: Cryoablation

CEM Cumulative equivalent minutes. Section 2.3.3. x

CT Computed tomography. x, xiii, 10

DSC Dice similarity coefficient. x, 15, Glossary: Dice similarity coefficient

ECoG Electroencephalography. x, 9

EF Epileptogenic focus. 9, Glossary: Epileptogenic focus (EF)

HGG High grade glioma. x, xvii, xviii, 7, Glossary: High grade glioma

HIFU High-intensity focused ultrasound. x, xiii, xv, 6, 15, Glossary: High-intensity focused ultrasound

icEEG Intracranial electroencephalogram. x, 9

iMRI Intraoperative MRI. x, 11, Glossary: Intraoperative MRI

LTTDM Lethal threshold temperature damage model. Section 2.3.4. x, 15

MRgLITT Magnetic resonance-guided laser induced thermal therapy. x, 1, 15

MRTI Magnetic resonance temperature imaging. x, xviii, 10, 14, 15, Glossary: Magnetic resonance temperature imaging

MWA Microwave ablation. x, 6, Glossary: Microwave

NMR Nuclear magnetic resonance. x, 10, Glossary: Nuclear magnetic resonance

PRF Proton resonance frequency. x, xvii, 10

RF Radiofrequency. x, xvi, Glossary: Radiofrequency

RFA Radiofrequency ablation. x, xvi, xvii, 6, 15, Glossary: Radiofrequency
**SRS** Stereotactic radiosurgery. x, 1, 8, *Glossary: Stereotactic radiosurgery*

**WBRT** Whole brain radiation therapy. x, 1, *Glossary: Whole brain radiation therapy*
Glossary

**Capacitive heating** Capacitive heating is a noninvasive modality of dielectric heating via electromagnetic waves. Capacitive heating is used to create hyperthermic temperatures, e.g., 42°C, in large body regions. For superficial applicators, designs include multiple channels arranged in multiple rings surrounding a length of axial body positions, e.g., three rings with four channels each. Within the rings, there is a bolus of deionized water to mediate power delivery. Devices’ power outputs are in the range of 400 W to 1600 W and oscillate at 100 MHz [1, 2]. There also exist interstitial applicators. x, 6

**Catheter-based ultrasonic device** An acoustic thermal ablation device that gains access to targets via body lumina, including major vasculature, or percutaneous minimally invasive surgery. These devices have a variety of designs that include independently operating elements that can be directed. Once the device is positioned, heat delivery takes about 10 min to 30 min. Since catheter-based ultrasonic devices are placed proximal to their targets, they use higher acoustic frequencies than high-intensity focused ultrasound (HIFU) and operate at 8 MHz to 10 MHz [3–5]. x, 6, 15

**Chemical ablation** Chemical ablation is the injection of substances, either acetic acid or more commonly ethanol, to induce tissue death. As an example, percutaneous ethanol injection (PEI) uses a 22-gauge needle to access a target lesion, commonly hepatocellular carcinomas. Through the needle, 2 ml to 5 ml of nearly pure ethanol is injected, depending on lesion size. The procedure requires multiple surgical sessions for efficacy. Guidance is via ultrasound or computed tomography (CT) [6, 7]. x, 6

**Critical structure** Critical structures are healthy tissues and/or organs that have been deemed essential to the patients survival or quality of life. A proposed intervention cannot impose undue damage to those tissues and/or organs. In radiation therapy, this concept manifests as dose limits. x, 2

**Cryoablation** Cryoablation uses interstitial probes to access target lesions. Liquid nitrogen or argon cool the tip to −125°C and −187°C, respectively. Argon-based devices have thinner diameters. Another innovation is the use of heated helium gas (67°C) in order to speed the necessary thawing [6, 8]. x
Dice similarity coefficient The Dice similarity coefficient (DSC) was proposed by Dice [9] and has been used extensively in imaging science. Its equation is defined in the text. The purpose of the DSC is to quantify the overlap of two binary masks. A valuable property of the DSC is that it does not count true negatives, i.e., coincident zero values in the binary masks.

Evidence-based medicine Evidence-based medicine is a preeminent idea in the healing arts that demands patient care decisions be driven by data. Common difficulties in following this simple idea is the dearth of definitive data or conflicting data. To resolve this dilemma, various experts and groups of experts have suggested hierarchies of data, called levels of evidence. An example of a lower level of evidence is a case study or medical practice guidelines informed by the gestalt of tradition. A high level of evidence is a randomized controlled trial; the highest level is usually considered a meta-analysis of randomized controlled trials. A capable introduction can be found in [10].

High grade glioma A classification of particularly dangerous primary brain neoplasms, i.e., anaplastic astrocytomas (Grade III astrocytoma) and glioblastomas (Grade IV astrocytoma). The same novel and standard of care interventions are often applied to both disease groups, so the classification of high grade glioma is used.

High-intensity focused ultrasound Modern HIFU uses phased array piezoelectric elements to direct acoustic waves into a target lesion. The purpose is either heating or mechanical disruption of the tissue. Heating can be for hyperthermia, ablation, or release of a targeting drug. Mechanical disruption is for the purpose of targeted drug release or transient tissue alteration, such as disrupting the blood brain barrier. HIFU is noninvasive, an obvious clinical boon. In order to reach the target tissue, acoustic frequencies are typically 1.0 MHz to 1.5 MHz with the extremes ranging from 0.6 MHz to 7 MHz [3].

Intraoperative MRI An iMRI suite is the combination of an operating room and a surgery-dedicated MRI. There exist iMRI designs that are expressly designed for neurosurgery, e.g., the BrainSUITE.

Irreversible electroporation A percutaneous ablation modality that uses electric pulses to introduce pores into affected cells. The pores undermine the homeostasis of the cells, leading to tissue ablation. A typical protocol uses 90 pulses of 70 µs to 100 µs,
1500 V to 3000 V, and 25 A to 45 A. As a non-thermal ablation modality, the theoretical advantage of irreversible electroporation is to enable physicians to ablate tumors even nearer to major vasculature than thermal ablation modalities [11,12].

**Isoeffect** Because thermal damage is realized through a time-temperature integrated process, different time-temperature histories can lead to the same biological/physiological effect. This engenders the idea of an isoeffect, where two heating histories can induce the same result, e.g., the same magnitude of cell kill in cultured Chinese hamster ovary cells [13].

**Magnetic resonance temperature imaging** There are an assortment of five major MR contrast mechanisms that can measure temperature [14, 15]. The most important for this dissertation is the proton resonance frequency (PRF) shift method. The other four are T1 relaxation rate, T2 relaxation rate, proton density-weighted images to measure available magnetization, and diffusion-weighted images to measure temperature-dependent diffusion rates. Each class of MRTI has an abundance of pulse sequences to interrogate the subject contrast. Near real-time temperature imaging, via phase contrast imaging to monitor PRF shift, empowers minimally invasive laser surgery.

**Microwave** Microwave (MW) refers to a broad and ill-defined bandwidth of the electromagnetic spectrum, depending on the particular field of science or engineering being considered. In medical hyperthermia, it refers to specific, approved frequencies of electromagnetic waves: 433 MHz, 915 MHz, or 2.45 GHz [6,16]. Interestingly, 2.45 GHz is found in consumer microwave ovens while 915 MHz is employed in larger commercial or industrial microwave ovens. MW ablation devices use interstitial waveguides that lead to antennae, introducing ablative electromagnetic waves. Compared to radiofrequency ablation (RFA), MW ablation typically uses fewer antennae than RFA uses electrodes. The MW antennae can heat further, i.e., 2 cm to 3 cm, and have directional antennae [16]. The peak power of MW ablation devices range from 50 W to 80 W.

**Nuclear magnetic resonance** Nuclear magnetic resonance is the fundamental physical phenomenon that once combined with spatial localization led to the advent of MRI. Lauterbur and Mansfield are credited with the application of magnetic field gradients to an NMR device for localization [17,18]. Ernst was also integral to the application of Fourier transform- based reconstruction in MRI [19]. The magnetic properties
of matter that were investigated via NMR are also in MRI, e.g., T1 and T2 rates’ dependence on temperature, magnitude of $B_0$, and physical arrangement. Nuclei with unpaired spins are available for NMR and MRI measurement. Experiments and techniques from NMR have been widely adapted for use in MRI, e.g., the Hahn echo of NMR is the spin echo of MRI [20]. Perhaps even more importantly, the proton resonance frequency (PRF) shift of water protons was discovered in NMR experiments and used in MRI [21].

**Radiofrequency** Radiofrequency (RF) refers to a broad and ill-defined bandwidth of the electromagnetic spectrum, depending on the particular field of science, industry, or engineering being considered. In medical hyperthermia and ablation, it refers to a narrower range of alternating current frequencies of 350 kHz to 500 kHz [8]. These alternating currents are emitted from or between interstitial electrodes which cause ablative heating. Some RFA devices have one electrode; some have many [6]. Relative other ablative modalities, RFA devices can have very high peak power outputs, in excess of 200 W.

**Stereotactic radiosurgery** Stereotactic radiosurgery (SRS) is a common intervention in the management of high grade glioma (HGG) and metastases. Unlike typical external beam radiation therapy regimes, SRS is delivered in one or a few fractions. It is carefully executed to ensure the highest possible precision, which necessitates a skull frame, same-day image simulation, and treatment planning. Dose depends on focal lesion size. In Andrews et al.’s randomized controlled trial, lesions with the broadest diameter $\leq 2$ cm were treated to 24 Gy, lesions with the broadest diameter 2 cm to 3 cm were treated to 18 Gy, and lesions $\geq 4$ cm were treated to 15 Gy [22]. SRS carries a risk for radiation necrosis. There are Co-60 and linear accelerator-based SRS systems.

**Temozolomide** This drug has been found to improve treatment of newly diagnosed high grade gliomas if administered concomitantly with SRS. This is standard of care and has a high level of evidence advocating its use [23]. Temozolomide has been investigated for the management of brain metastases; however, efficacy is marginal [24].

**Temperature probe** This is a broad reference to thermocouples and flouroptic temperature probes. In experiments, temperature probes are used interstitially in experiments.
to validate magnetic resonance temperature imaging (MRTI) [14]. In the clinic, temperature probes can be integrated with a thermal applicator, e.g., the Monteris laser applicator [25]. x, 14

**Thermochemical ablation** This is the injection of a neutralized acid-base mixture. The acid-base mixing occurs within a catheter immediately before introduction into the target tissue. The resulting mixture is a salt solution hot enough to induce thermal ablation. [26]. x, 6

**Whole brain radiation therapy** Whole brain radiation therapy (WBRT) is a common intervention in the management of high grade glioma (HGG) and brain metastases. WBRT is delivered over 3 to 4 weeks for a total of about 35 Gy in the whole brain [22]. WBRT has been found to suppress the development of new neoplasms, improving progression free survival. Unfortunately, WBRT can induce psychological symptoms. In present management of HGG and brain metastasis, WBRT is always paired with SRS. x
Chapter 1

Introduction

Magnetic resonance-guided laser induced thermal therapy (MRgLITT), an emerging minimally invasive procedure, has curried interest in the neurosurgery community as a tool to treat metastases, primary cancers, radiation necrosis, and epilepsy. Based on reviews of brain metastasis incidence data, Eichler and Loeffler estimate the annual incidence of brain metastasis to be nearly 200,000 cases per year and 8% to 10% of adults who ever suffer cancer will present with symptomatic brain metastases [27]. Patients receiving surgical resection of metastases live significantly longer—median survivals of 11 months versus 3 months [28, 29]. Also, palliation of brain metastases improves neurological symptoms, improving quality of life and transcending a sense of therapeutic nihilism in the face of poor survival statistics [30]. In addition to metastases, some 22,850 primary cancers of the central nervous system occur, mostly in brain [31]. Of these, more than 14,000 are high grade gliomas (HGG) [32–34].

For malignant brain neoplasms, a chief intervention in the standard of care armamentarium is external beam radiation therapy, delivered as either whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) or both (WBRT+SRS) [27,35]. Using MRI to image 516 metastases after SRS, evidence of recurrence or radiation necrosis, a serious complication, appears in up to 30% of treated lesions [36]. Both conditions typically demand aggressive management, in context of the patient’s health. More widely considered, incidence of symptomatic radiation necrosis ranges from 2% to 17% depending on the
radiation therapy delivered and disease state [27].

In addition to primary neoplasms, metastases, and radiation necrosis of the brain, MRgLITT has been identified to treat a fourth malady of the brain, epileptogenic foci [37–45]. Epilepsy has an incidence of about 150,000 per year [46]. Of these, an estimated 20% to 40% of patients’ epilepsy is not well managed via pharmaceuticals [47–50]. For these medically intractable cases, surgery is a possible intervention, albeit carefully considered [51, 52]. Together, these conditions represent a host of patients who stand to benefit from MRgLITT and would otherwise have limited treatment options. The primary advantages of MRgLITT over traditional interventions are brief hospitalizations, reduced risk of surgical complication, no ionizing radiation, and the possibility of retreatment as necessary [53–55].

While the laser applicator’s placement is guided by MR imaging, deciding the laser’s intended placement is exclusively driven by the physician’s prerogative and experience. An accurate computational model that can \textit{a priori} predict the laser’s heating improves surgical planning by indicating the location and number of required laser applicators [56, 57]. This information would effectively minimize the incidence of unsatisfactory laser applicator placements, either because of inadequate target coverage or unacceptable heating of critical structures. There are a number of significant challenges that prevent accurate \textit{a priori} planning from entering common clinical practice, including the following: lack of accurate bioheat and optical properties [58, 59], accounting for nonlinear bioheat and optical properties [60–63], heterogeneous bioheat and optical properties [62], convective boundary conditions [64], and approximations of laser-tissue interactions [57, 65]. In order to expedite the conception and implementation of a clinically useful MRgLITT planning algorithm, a train-and-predict paradigm is adopted.
Figure 1.1: This flowchart describes the first-line treatments available for metastatic brain tumors, which are surgical resection and stereotactic radiosurgery [35]. Surgical resection tends to be more appropriate for larger, more accessible tumors, while stereotactic radiosurgery is for smaller and deeper metastases. If there are multiple metastases present, both interventions may be given. Following stereotactic radiosurgery, there is a risk of radiation necrosis, which also may require surgical resection.

1.1 Hypothesis

Computational modeling techniques can create thermal predictions for MR-guided laser induced thermal therapy matching the MR temperature imaging with a Dice similarity coefficient greater than 0.7 with a $\geq 95\%$ probability.
1.2 Specific aims

The following specific aims are designed upon a well-accepted framework of predictive model-building, described by Oden et al. [66].

1. **Sensitivity and uncertainty analysis:** Stochastic simulations will propagate the uncertainty found in the literature parameters into probabilistic predictions, demonstrating the bioheat transfer equation’s sensitivity to parameter variance.

2. **Model calibration:** Models of varied complexity will be trained on MR temperature imaging of clinical laser ablations.

3. **Simulated model validation:** Leave-one-out cross validation will compare the simulated predictive performance of the trained models and a model using naïve literature values.

1.3 Dissertation organization

This dissertation begins with a brief, need-driven justification for the work. The second chapter is a review of salient information. The third chapter is a publication addressing the first specific aim [59]. In Chapter 3, a transient finite element method (FEM) model is used. Aims 2 and 3 are found in Chapters 4 and 5; both Chapters have both model calibration and validation, but consider different models. The fourth chapter is a publication and is also the calibration and validation of the FEM model [67]. The fifth chapter is previously unpublished work and is the calibration and validation of a surrogate model for the FEM model. The sixth and final chapter is Discussion. Appendix A lists the clin-
ical ablation data used in Chapters 4 and 5; Appendix B displays results from Chapter 5 demonstrating a model’s convergence and alternative objective functions. Appendix C compares the transient finite element method model of Chapter 4 and the steady state of Chapter 5 as directly as possible. The PDF document is richly linked using the \texttt{hyperref} package in \LaTeX. The reader may quickly view a list of abbreviations, a glossary, a list of mathematical notation, and PDF bookmarks for chapters, sections, and subsections. If the reader is following a link to the Bibliography, it is recommended that he or she use \texttt{Alt+Left Arrow}, the present MS Windows hotkey in Adobe Reader or Acrobat, for a quick return to the previous view in the PDF document.
Chapter 2

Background

The oncological application of heat has roots deep in history, as early as 5000 years ago [68]. The Edwin Smith Surgical Papyrus is an Egyptian medical text of 48 case studies, including the use of hyperthermia in breast cancer [69, 70]. The text is dated within a few hundred years after the emergence of Egyptian writing itself [71]. Beginning in the 1600s, many physicians have recorded tumor regression in pyrexic patients [72]. By the 1880s, such observations created impetus for Coley to administer a toxic concoction of sterile bacteria to patients, inducing fever in order limit cancer growth [73]. While Coley’s *modus operandii* conflated hyperthermia with immunomodulation [74], Westermark was the first to isolate the application of heat as a cancer therapy, published in 1898 [75]. Westermark’s method was to circulate heated water through containers that were in contact with inoperable uterine carcinomas. The water’s temperature was 42°C to 44°C, remarkably within the useful hyperthermic temperature ranges identified by careful, modern experimentation [68, 76–83].
2.1 Hyperthermia, ablation, and minimally invasive interventions

In present use, the therapeutic heating of tissue to supraphysiological temperatures has two primary regimes: hyperthermia and ablation. They are defined by the length time for heating and the magnitude of the heating. Hyperthermia is characterized by lower temperatures, i.e., 40 °C to 46 °C, and longer times, 0.5 h to 5 h [78]. In clinical use, these ranges are narrowed depending on the purpose of the heating — 40 °C to 44 °C and 30 min to 90 min [1,83–85]. Conversely, ablation is characterized by higher temperatures and shorter heating times. The typical temperatures and times in ablation are modality-dependent.

The contemporaneous use of hyperthermia is not as a standalone therapy and is instead an adjuvant to other interventions, namely radiation therapy, chemotherapy, or immunomodulation and eclectic combinations thereof [86–92]. Hyperthermic temperatures can modify the tissue environment in a variety ways, including signal modulation, blood perfusion increase, and biomechanical modification of tumor microenvironment [91,93]. The addition of heat is intended to improve the therapeutic margin of the adjuvant interventions, as some animal model studies dramatically demonstrate [90]. Contemporary hyperthermia protocols in humans involve regional hyperthermia, e.g., heating a thigh or pelvis. Regional heating methods include radiative heating or capacitive heating [86,94].

In contrast to hyperthermia, thermal ablation exists as a primary intervention in vast array of body sites, and can be the preferred intervention when the lesion is deemed inoperable or the maximum radiation dose has been delivered [6]. There are a plurality of catheter-based, percutaneous ablative devices and even a noninvasive ablation modality, high-intensity focused ultrasound (HIFU). The list of percutaneous thermal interventions includes radiofrequency ablation (RFA), microwave ablation (MWA), laser, catheter-based ultrasonic devices, thermochemical ablation, and cryoablation (CA). Along with the thermal percutaneous interventions, the following nonthermal percutaneous modalities compete
for consideration in the same clinical uses: chemical ablation and irreversible electroporation. A chosen modality for ablation rarely has a high level of evidence demonstrating its primacy in terms of common efficacy measures, e.g., two-year survival or overall survival or progression free survival. Even when randomized controlled trial data comparing ablative modalities to each other and/or surgical resection are available, the conclusion is not always definitive or else new emerging modalities need evaluation as well, ergo mitigating the finality of conclusions [11,95–101]. While the medical research literature does not represent a canon advising a particular modality, minimally invasive ablative modalities pose many advantages over surgical resection. Namely, morbidity and cost can be reduced in traditional surgical targets while introducing new surgical targets only accessible via these minimally invasive procedures.

2.2 MR-guided laser induced thermal therapy in brain

Magnetic resonance-guided laser induced thermal therapy (MRgLITT) is a particular realization of image-guided, minimally invasive thermal ablation. It has found utility in a variety of body sites, and significant interest for brain [102]. As explained in Chapter 1, MRgLITT in brain has significant research efforts to ameliorate primary cancers, metastases, radiation necrosis, and epileptogenic foci. The following subsections address the standard of care for the aforementioned ailments and the surgical technique of MRgLITT.

2.2.1 MRgLITT in oncology

Management of high grade gliomas (HGG) and secondary tumors in the brain are among the most difficult challenges in medicine [31,35]. Like much of oncology, treatment of brain neoplasms is characterized by radiation, chemotherapy, and surgical resection [35,103]. Unfortunately, therapeutic improvement is made in small steps and in very specific disease states in order to maintain a high level of evidence. Examples include dose-finding for
targeted therapy of HGGs [104], the addition of adjuvant chemotherapy [105], using meta-
analysis to evaluate traditional interventions at a high level of evidence [23], or novel
measures of progression and response to better consider concomitant interventions [106].
Given the poor prognosis of both HGGs and brain metastases, there are a plurality of
investigative interventions with targeted therapy/immunomodulation drawing significant
interest [24,107].

In context of other treatments for brain neoplasms, the comparative effectiveness of
MRgLITT is not in a position to be evaluated. Presently, the safety of MRgLITT has
been well demonstrated, and some prospective patient recruitment has been done. The
ability for MRgLITT to access deep tumors and re-treat lesions as they emerge makes
MRgLITT a favorable surgical intervention for the management of aggressive brain neo-
plasms [55, 108–112]. Explicitly, the surgical trauma burden associated with MRgLITT is
small enough that physicians have deemed repeated ablations are warranted in order to
extend life and improve quality of life. For the time being, all patients receiving MRgLITT
have already undergone first-line therapies — stereotactic radiosurgery (SRS) with con-
comitant temozolomide and/or surgical resection [35] — or have been critically evaluated
for first-line therapies.

Significant work in treating HGG with MRgLITT has been accomplished by a multi-
institutional, interdisciplinary team, including neurosurgeons, neuroradiologists, radiation
oncologists, and medical oncologists [111]. Mohammadi et al. represents the best attempt
to document the treatment of HGGs with MRgLITT to date. Patients were retrospectively
analyzed. Of 34 treated patients, 12 had died after 7.2 months. 10 succumbed to disease
progression and two from other causes. 13 ablations were considered conformal to the
target and were shown to have statistically better progression-free survival. The primary
conclusions were that (1) better long-term control, defined by progression-free survival and
survival, was achieved by conformal laser heating versus nonconformal ablation and (2)
some HGGs were amenable to conformal laser delivery. Comparative effectiveness to other
interventions was beyond the scope of the study. A dangerous side effect of radiation therapy in the brain is radiation necrosis. The incidence of radiation necrosis is not widely tracked, but disparate studies report incidence rates of 2% to 17% and climb as high as 30% in previously untreated patients [27,36]. A 5% to 10% incidence rate of symptomatic radiation necrosis in de novo patients receiving radiation therapy seems plausible [113]; it is suffice to accept the incidence of radiation necrosis in brain to be a small but appreciable fraction of radiation therapy patients. Patients who have already undergone SRS, are treated to 16 Gy to 22 Gy, or have large treatment volumes are at considerably greater risk of radiation necrosis with rates up to 50% [113,114]. Patients afflicted with radiation necrosis benefit from surgical treatment if they are otherwise not imminently threatened — i.e., Karnofsky performance status > 70, control of extracranial disease, > 3 months life expectancy [109,112]. MRgLITT is well positioned to treat patients with many previous surgical and radiation interventions; their wound healing is likely compromised, making MRgLITT an appealing treatment option over traditional resection [113]. There is a growing number of investigations where MRgLITT has treated radiation necrosis [109,112,115,116] in addition to reviews [113,117].

2.2.2 Epileptogenic foci

A significant fraction, ~20% to 40%, of epilepsy patients are pharmaco-resistant [47–50]. Consequently, these patients may be considered for surgery to ameliorate seizures with about 50% being eligible for operation [118]. However, given the inherent risks of neurosurgery, surgical patients typically have debilitating symptoms and targets amenable to surgery. Epilepsy control outcomes depend on the site of operation [118], but will be considered as one group for this discussion. Surgery can provide good control at early time points — between 60% and 70% seizure control for the first two years [118] — but the efficacy of surgery is not definite with about half of surgical patients having epileptic relapse at five and ten years’ follow-up [118]. Nonetheless, compassionate care can demand
drastic intervention in the face of intractable epilepsy and even significantly reduce the costs of patient management [50]. Furthermore, there is evidence that epilepsy control is underutilized and neurologists overestimate the risks of the operation [119–123].

The surgical target in epilepsy surgery is known as an epileptogenic focus (EF) or foci. A primary method to localize EF is intracranial electroencephalogram (icEEG). icEEG can create image-like maps called electrocorticography (ECoG) for localizing EF and studying human cognition in general [124]. ECoG has high spatio-temporal resolution and can be registered with anatomical MR scans. An example clinical ECoG spatio-temporal resolution is $\sim 1\text{ mm}$ with sampling rates of $\sim 1.0\text{ kHz}$. Considerably faster sampling rates are possible but result in prohibitively large datasets. icEEG is invasive and takes a considerable amount of time of hospitalized monitoring, up to two weeks [125], to adequately localize EF.

Minimally invasive interventions are an attractive method to reduce surgical trauma and increase the therapeutic margin of epilepsy surgery, with MRgLITT being a leading novel modality [43, 117]. There are a growing number of publications documenting its use [37–42, 44, 45]. The results are promising, but nuanced by the realities of epilepsy management. Generally, there are three post-operative seizure outcomes.

1. Patients were seizure-free.

2. Patients derived meaningful seizure control and/or their condition was well controlled by drugs after surgery.

3. The patients conditions remained intractable.

For MRgLITT epilepsy surgery to become preferred to techniques involving craniotomy, MRgLITT will need to be demonstrated to have better control or fewer side effects in a randomized controlled trial. Regarding the possibility of improved efficacy, improvement of non-invasive EF localization would behoove MRgLITT epilepsy surgery. The listed publications of MRgLITT epilepsy surgeries use non-invasive localization methods, since
performing a craniotomy and subsequent icEEG would nullify non-invasive benefits of MR-gLITT. Namely, the MRgLITT investigators use permutations of video electroencephalogram (EEG), MRI, FDG-PET, SPECT, and Wada testing. At present, MRgLITT epilepsy surgeons are not using the gold standard localization technique, icEEG-based ECoG. A new avenue for non-invasive localization is coincident PET/MR [126]. However, the potential for minimally invasive operation is compelling enough for surgeons at specialized epilepsy centers to investigate MRgLITT.

2.2.3 Imaging and surgical technique

The two features that empower MRgLITT are stereotactic surgery and real-time temperature measurement via MR. Stereotactic laser techniques were first used in the brain and guided via CT [127]. MR-monitored laser-tissue effects were well explored by Jolesz et al. [128]. Their investigation described MRTI contrast mechanisms that were T1- and T2-weighted. The methods clearly showed changes, but the practical utility was limited by the hysteresis of T1 and T2 in heat shocked tissues and the need to observe the cooling in order to demonstrate degree of thermal insult. Later, proton resonance frequency (PRF)-shift thermometry was co-opted from nuclear magnetic resonance (NMR) [21] and described by Ishihara et al. and De Poorter et al. [129–131]. Real-time PRF-shift thermometry provides a robust, linear relationship to monitor temperature in MRgLITT. The challenges of PRF thermometry include lipid-rich tissue and motion [15]. Both challenges have their own extensive bodies of research addressing them, e.g., [132,133].

The combination of effective MRTI and stereotaxis led to the advent of modern MR-gLITT. There are two major laser applicator vendors: Monteris Medical NeuroBlate® and Medtronic Visualase®. Chapters 3, 4, and 5 of the dissertation will focus on the Visualase® device; a device description can be found in Chapter 3. The following description of MR-gLITT is based on sundry publications, some that describe the MR suite being separate from the neurosurgery operating room [39] and some utilizing an intraoperative MRI (iMRI).
The positive impact of an iMRI is well described by Hawasli et al. [110]. They planned four surgeries that used multiple bore holes. However, they had two more surgeries where a single bore hole was indicated in pre-surgical planning, but additional bore holes we deemed necessary mid-procedure. The presence of an iMRI enabled the addition of more bore holes, without undue extension of the operation’s time length. Without an iMRI, the alternative is to shuttle the patient between the neurosurgery operating room and the reserved diagnostic MRI, while under anesthesia and with implanted laser applicator(s). Accurate computational models for planning would reduce the necessity of changes to the surgical plan. Critically, this advantage is exaggerated in cases where the neurosurgery operating room is separate from the MR suite. More about the technique is described in Chapters 3 and 4.

2.3 Thermal damage models

2.3.1 Arrhenius process

As Dewhirst et al., Pearce, and Dewey elegantly describe in their reviews [78, 83, 134], thermal damage manifests through a time-integrated Arrhenius rate process given by

$$\Omega = \ln \left( \frac{c(t)}{c(t_0)} \right) = \int_{t_0}^{t} A \exp \left( \frac{-E_a}{RT(\tau)} \right) d\tau$$

(2.1)

where \( t_0 \) and \( t \) respectively are the initial and end time points. \( \Omega \) is a ratio of the endpoint concentration of native/unablited proteins, \( c(t) \), to initial proteins, \( c(t_0) \). \( A \) is the frequency factor, \( R \) is the universal gas constant, \( E_a \) is the activation energy of the protein’s transition of state, and \( t \) is the absolute temperature. \( E_a \) and \( A \) are empirical and vary with whatever process the investigator is interested, e.g., transepidermal necrosis in porcine model [135].
2.3.2 Thermal dose: an example

The first obvious implication of Equation (2.1) is that there are myriad combinations of time and temperature that arrive at the same value of $\Omega$. Chicken eggs have been used by many hyperthermia/ablation investigators to model the time-temperature-dependent coagulation process, e.g., [128, 136]. As a heuristic example, consider cooking an egg. A chicken egg from the grocery store can experience the four following elevated temperature regimes: low heat with short time or pasteurization, $60^\circ C$ for 3.5 min; moderate heat for a long time like sous-vide, $62.8^\circ C$ for 0.75 h to 2.0 h; high heat for a short time like scrambled or fried eggs, $> 71.1^\circ C$; and finally excessive and charring heat, $> 250^\circ C$ for 2.0 min for a few seconds [137–139]. These temperature regimes are an excellent demonstration the time-history qualities of hyperthermia and ablation.

The pasteurization case illustrates a heat shock that is intended to kill *Salmonella* bacteria but does not perturb the egg because the heat shock is sub-coagulative to the egg. The clinical analog is a temperature range of $37^\circ C$ to $40^\circ C$. While it is conceivable that such a small temperature rise may increase blood perfusion and marginally gain the benefits of hyperthermia, $< 40^\circ C$ is not clinically used.

The sous-vide case is analogous to hyperthermia, where the coagulation process is gradual and takes a very long time to become terminal. Critically, an egg has different components, i.e., the white and the yolk, that have different activation energies, $E_a$. For the sous-vide case, the difference in $E_a$ engenders a coagulation rate difference between the white and the yolk. At 45 min, the white is appreciably coagulated, while the yolk yet flows. By 2.0 h, both egg components are nearly terminally coagulated. This state transition is exactly described by Equation (2.1) since the concentration of denatured protein dominates the log ratio of

$$\Omega = \ln \left( \frac{c(t)}{c(t_0)} \right).$$

With extended heating, $\Omega$ may continue to rise prodigiously, but the quantity of mass of
native protein transitioning into a denatured state is vanishingly small. The quantity of $\Omega$ is really only meaningful at the lower range, i.e., less than 2.3. In Pearce’s 2013 review [82], it is pointed out that thermal damage is detectable in histology with about $\frac{c(t)}{c(t_0)} \approx 90.5\%$ or $\Omega = 0.1$ and a “sure kill” in all tissue types corresponds to $\frac{c(t)}{c(t_0)} = 10.\%$ or $\Omega \approx 2.3$. Again, in the clinic, the hyperthermia temperature regime is implemented as an adjuvant to a primary intervention. Typically, the denaturation of proteins — the accumulation of $\Omega$, i.e., thermal dose — is not the direct goal of clinical hyperthermia.

Next, a fried egg only needs to reach an excessively hot temperature and total coagulation is essentially immediately complete; this is analogous to thermal ablation. Through these culinary examples, a second obvious implication of Equation (2.1) is that there is an effect limit of hyperthermia and ablation. Once enough native protein has denatured, the tissue is irreversibly damaged and further application of heat has no effect. This is in contrast to other interventions like radiotherapy where excessive dose in the target is not the limiting factor; radiation dose is limited by the tolerance of healthy tissue and accuracy of treatment delivery.

Finally, excessive heating is undesirable in cooking an egg because it burns. Furthermore, pyrolyzation the egg creates mutagens [137]. Likewise in ablation, temperatures near and beyond 100°C create vaporization or charring that result in patient complications, damage to the percutaneous applicator, and/or tissue changes that undermine the intended heat delivery. To avoid deleterious high heat, both hyperthermia and ablation use control points where the temperature is not allowed to exceed a certain value. Control points are monitored via MRTI or temperature probes within the interstitial applicator.

### 2.3.3 Cumulative equivalent minutes

Another means to describe thermal damage is the cumulative equivalent minutes (CEM) model, described in [78, 82, 83, 134]. The fundamental idea is to quantify the amount of time a subject must be held at a constant temperature in order to generate an isoeffect
compared to a standard temperature, often 43°C. This leads to an equation that allows the conversion from an applied temperature for an applied time to be compared to the standard temperature in a standard time increments, i.e., 1 minute. For the case of the standard temperature being 43°C, it is

$$CEM_{43} = \int_{t_0}^{t} (R_{CEM})^{(43°C - T(\tau))} d\tau$$

(2.2)

where $CEM_{43}$ is the number of minutes at 43°C required to match an isoeffect generated by holding the subject at a different temperature, $T$ in °C, for time, $t$ in minutes. The choice of the standard temperature being 43°C is informed by Sapareto et al.’s work [13]. At all hyperthermic temperatures, the rate of cell kill is exponential with temperature. However, in the case of Chinese hamster ovary cells, the exponential base, $R_{CEM}$, below 43°C is smaller than above 43°C. This transition temperature is called the breakpoint in hyperthermia parlance. In Sapareto’s review [76], the exponential base is modeled as a discrete transition from 0.25 to 0.50 as temperature increases beyond 43°C. Dewhirst et al. indicates that while the standard temperature could always be the breakpoint temperature of the target, it is more convenient for researchers and clinicians to choose a broad standard which is 43°C [78]. The value of $R_{CEM}$ varies depending the tissue or cell line and whether the heat shocked sample is in vivo or in vitro [78]. Traditionally, $R_{CEM}$ is 0.25 and 0.50 for values below and above 43°C, respectively.

### 2.3.4 Lethal threshold temperature

Since page 13, this dissertation has used data-driven arguments to extol the use of thermal damage models that incorporate time-temperature history — namely, Equations (2.1) and (2.2). However, in the case short ablations, a lethal threshold temperature damage model (LTTDM) can delineate between live and dead tissue after the heat shock. Given the importance of time-temperature models, clearly, the meaning and context of “short”
and “ablation” require explanation. “Ablation” immediately precludes any hyperthermia. “Short” would be \( \leq 2.0 \) min for the entire heat delivery. That forbids LTTDM’s application to ablations that are either several minutes, the sum result of repeated short ablations, or steered applicators — e.g., RFA, most HIFU, catheter-based ultrasonic devices, and steered laser ablations. Despite the list of limitations, the LTTDM is applicable to Medtronic’s Visualase\(^\text{R} \) (Louisville, Colorado) laser applicator for use in magnetic resonance-guided laser induced thermal therapy (MRgLITT).

Yung et al. investigated the use of the three damage models — Arrhenius, Section 2.3.1; CEM, Section 2.3.3; and LTTDM — to each other in four laser-ablated \emph{in vivo} normal canine brains [140]. It is critical to recapitulate their work as a justification for using the LTTDM. In the experiments, the laser ablations were monitored by real-time MRTI, providing the necessary temperature information to make damage predictions. For each damage model, the demarcation of live or dead was allowed to vary. Namely, the Arrhenius process damage model’s prediction of dead tissue was thresholded by \( \Omega \), and the value of \( \Omega \) varied from 0.01 to 10.2. Secondly, the CEM model’s damage prediction was thresholded between 10 CEM\(_{43}\) and 1200 CEM\(_{43}\). Thirdly, the temperature threshold for the LTTDM was varied between 51 and 71 °C.

For the many different predictions made by the three damage models, a regional comparison was made to post-ablation, post-contrast T1-weighted images, a recognized surrogate of evaluating the extent of ablation [141]. The comparison was made via Dice similarity coefficient (DSC). Yung et al. reported the maximum DSC possible for each of the three models as well as the DSC by using previously cited damage thresholds. The result was the maximum DSC achieved by the three damage models had the same mean and similar standard deviation. Furthermore, the DSC values calculated by using the previously cited damage model parameters were very close to the maximum possible. In summary, for the case of short ablations, all three damage models matched the post-ablation, post-contrast T1-weighted image — the study’s gold standard — and robustly produced high
DSC values for a variety of damage model threshold choices.
Chapter 3

Generalised polynomial chaos-based uncertainty quantification for planning MRgLITT procedures

This Chapter is a near-verbatim quotation of Fahrenholtz et al. [59]. The Chapter uses English grammar and spelling of the United Kingdom. The only intended modifications are the numbering of citations, equation numbers, figure numbers, table numbers, and section numbers. The citations are numbered according to the dissertation, as opposed to the quoted journal article. Among the Specific Aims, this Chapter addresses Aim 1. Its citation, according to the Informa Healthcare format, is thus:


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3.1 Abstract

*Purpose:* A generalised polynomial chaos (gPC) method is used to incorporate constitutive parameter uncertainties within the Pennes representation of bioheat transfer phenomena. The stochastic temperature predictions of the mathematical model are critically evaluated against MR thermometry data for planning MR-guided laser-induced thermal therapies (MRgLITT). *Methods:* The Pennes bioheat transfer model coupled with a diffusion theory approximation of laser tissue interaction was implemented as the underlying deterministic kernel. A probabilistic sensitivity study was used to identify parameters that provide the most variance in temperature output. Confidence intervals of the temperature predictions are compared to MR temperature imaging (MRTI) obtained during phantom and *in vivo* canine (*n* = 4) MRgLITT experiments. The gPC predictions were quantitatively compared to MRTI data using probabilistic linear and temporal profiles as well as 2-D 60°C isotherms. *Results:* Optical parameters provided the highest variance in the model output (peak standard deviation: anisotropy 3.51°C, absorption 2.94°C, scattering 1.84°C, conductivity 1.43°C, and perfusion 0.94°C). Further, within the statistical sense considered, a non-linear model of the temperature and damage-dependent perfusion, absorption, and scattering is captured within the confidence intervals of the linear gPC method. Multivariate stochastic model predictions using parameters with the dominant sensitivities show good agreement with experimental MRTI data. *Conclusions:* Given parameter uncertainties and mathematical modelling approximations of the Pennes bioheat model, the statistical framework demonstrates conservative estimates of the therapeutic heating and has potential for use as a computational prediction tool for thermal therapy planning.
3.2 Introduction

Magnetic resonance-guided laser-induced thermal therapy (MRgLITT) is a minimally invasive ablative procedure that can rapidly (< 180 s) deliver heat to treat focal cancerous lesions or radiation necrosis in the brain [115, 142]. The optical fibre is placed through a burr hole into the target disease via stereotaxy, analogous to an image-guided stereotactic biopsy [108, 142]. MRgLITT for patient-specific treatment of focal cancerous lesions in brain presents an attractive treatment option with significantly less impact on the patient compared to conventional surgical procedures. For many anatomical sites of interest, magnetic resonance image (MRI) guidance provides a means for planning, targeting, monitoring and verifying the delivery of these therapies in a single, closed-loop session. To this end, several FDA-cleared MRgLITT systems (Monteris www.monteris.com, Visualase www.visualaseinc. com) have become commercially available. These systems facilitate MRgLITT procedures on any modern clinical MRI scanner and are currently in post-market studies at multiple institutions [37, 55, 108, 142–146]. The goal of the therapy is to treat a targeted tissue volume, < 3 cm in diameter, in such a highly controlled manner so as not to incur damage to nearby normal tissue structures which would result in complications.

Proton resonance frequency-based thermometry or magnetic resonance temperature imaging (MRTI) provides a means to real-time monitor the heat distribution during the therapy [147, 148]. MRTI's temperature information improves the safety and efficacy of MRgLITT by allowing the physician to avoid overheating, tissue vaporisation, and charring near the laser and prevent treating tissue beyond disease extent. However, in the current paradigm, visual assessment of multiple structures in multiple planes, even with the aid of user-assigned critical monitoring points, presents a delivery paradigm that is inherently difficult to manage. Integration of mathematical modelling and computational science techniques with the clinical imaging information available may prove useful for MRgLITT before and during the procedure, either by predicting the result of a treatment before the
surgery, or during surgery to improve MRTI and robustly estimate lost information due to data corrupting motion, low signal-to-noise-ratio (SNR), excessive heating, and catheter-induced signal voids [149–152]. These enhanced realtime monitoring approaches may further assist in more safely and accurately controlling therapy delivery for increased efficacy of the procedure [153, 154]. The availability of increasingly powerful high performance and portable computing resources, such as NVIDIA® graphics processing units (GPUs) [155] and Intel® many integrated core (MIC) architecture [156], indicates that the presence of computational science is likely to continue escalating in these image-guided thermal therapy procedures.

The development of computational tools for planning hyperthermia and ablation therapies has received significant attention for improving therapy outcomes [4, 61, 147, 157–159]. With predictive modelling, the laser fibre placement can be planned in a virtual environment to improve the likelihood of a successful and short treatment. A common method for predictive modelling of the distribution of induced heating in blood perfused tissue is the Pennes bioheat transfer equation (BHTE) [160] solved with a finite element method (FEM) [60, 62, 65]. A difficulty in obtaining accurate results from the BHTE is the uncertainty incurred by using homogeneous literature values of biothermal and optical constitutive values for patient-specific planning. Uncertainty is further increased with incorporating the additional complexity of investigating the non-linear effects of temperature-dependent or thermal dose-dependent constitutive parameters.

Truly predictive prospective computer modelling requires substantial validation efforts and novel computer modelling techniques that incorporate the inherent uncertainties of the computer model into the predicted solution [161–163]. Monte Carlo modelling is the quintessential example of incorporating uncertainty into the computer model output. While a Monte Carlo approach would provide the necessary probabilistic outputs, the computational cost required to simulate a sufficient number of realisations is large. There exist methods to improve the convergence of Monte Carlo through the quasi-Monte Carlo
method, Latin hypercube sampling, and the Markov Chain Monte Carlo method [164–168].

Another successful technique to accelerate uncertainty quantification (UQ) is generalised polynomial chaos (gPC) expansion. gPC provides a means of providing the model with UQ prodigiously faster than Monte Carlo for computations using few random input variables, i.e. < 10 variables. gPC is originally based on the work of Wiener [169]. This method used a high order Hermite polynomial as a spectral approximation for model outputs. Nearly 50 years later, Ghanem and Spanos identified the spectral approximation as a viable tool in FEM modelling of stochastic differential equations [170]. Xiu and Karniadakis demonstrated that the convergence of spectral methods for solutions to differential equations were optimised by matching certain input functions’ distributions with corresponding output polynomials, known as the Wiener-Askey scheme [171]. For similar diffusive type equations, gPC’s convergence to a mean solution, $N < 10$ realisations, compares exceptionally favourably, pointwise error < 1.E-2, when compared with Monte Carlo’s $N = 20 000$ realisations [171,172]. gPC has already been applied to an eclectic list of studies. The topics include radiation oncology, combustion modelling, nuclear reactor design, and robotic dynamics on rugged terrain [173–176].

Here we investigate the use of a stochastic form of the BHTE coupled to a diffusion theory approximation of light transport in tissue for improving the decision-making utility of thermal modelling. Temperature-dependent constitutive values are mathematically characterised via an assumed probability distribution providing the ability to perform uncertainty quantification via generalised polynomial chaos and provide quantitative confidence levels in the computer model predicted temperature for each spatial location at each time point.
3.3 Methods

3.3.1 Mathematical model of uncertainty

Ignoring discretisation errors, computer implementations of mathematical models fundamentally have uncertainty in their representation and predictions of physical phenomena \cite{66} due to two dominant sources of inherent variability. (1) Simplifications are needed to make the algorithm practical. For example, in this work we employ a Pennes bioheat transfer equation (Equation 3.1) with a perfusion term that represents the manifestation of a complex and tortuous microvasculature on the bulk continuum scale heat transfer. (2) The computer model parameters are not known precisely. In this application, optical and biothermal parameters are taken from literature values and are empirical representations of non-linear temperature and damage-dependent phenomena. Further, the parameters fail to incorporate patient- and tissue-specific variability resulting from heterogeneities.

This investigation aims to manage model parameter uncertainty associated with a stochastic form of Pennes bioheat transfer equation for blood perfused tissues (Equation 3.1). The motivating idea is that the Pennes’ representation of the physics of the bioheat transfer phenomena coupled with statistical methods of uncertainty quantification may synergistically provide a reliable prediction model regardless of constitutive parameter uncertainties and mathematical modelling approximations.
\[
\rho c_p \frac{\partial u}{\partial t}(\vec{x}, t, \vec{Z}) - \nabla \cdot (k(\vec{Z}) \nabla u) + \omega(\vec{Z}) c_{\text{blood}} (u - u_a) = \mu_a q_{\text{laser}}(\vec{x}, t, \vec{Z})
\]

\[
q_{\text{laser}}(\vec{x}, t, \vec{Z}) = \int_{U_{\text{tip}}} \frac{P(t)}{V_{\text{vol}}(U_{\text{tip}})} \frac{3 \mu_{\text{eff}} \exp(-\mu_{\text{eff}}|\vec{x} - \vec{\xi}|)}{4 \pi |\vec{x} - \vec{\xi}|} d\vec{\xi}
\]

\[
\vec{x} \in U \setminus U_{\text{tip}} \quad \mu_{\text{tr}} = \mu_a(\vec{Z}) + \mu_s(\vec{Z}) (1 - g(\vec{Z})) \quad \mu_{\text{eff}} = \sqrt{3 \mu_a(\vec{Z}) \mu_{\text{tr}}}
\]

\[
\Omega(t) = \int_0^t A e^{-\frac{E_A}{R u(t)}} d\tau - k(\vec{Z}) \nabla u \cdot \vec{n} = 0 \quad \text{on } \partial U
\]

\[
\vec{Z} \equiv (Z_k, Z_{\omega_{\text{native}}}, Z_{\omega_{\text{coag}}}, Z_g, Z_{\mu_{a_{\text{native}}}}, Z_{\mu_{a_{\text{coag}}}}, Z_{\mu_{s_{\text{native}}}}, Z_{\mu_{s_{\text{coag}}}})
\]

Here, \(\rho\) is the tissue density, \(c_p\) is the specific heat of tissue, \(k\) is the tissue conductivity; \(\omega\) is the tissue micro perfusion primarily due to capillaries, \(c_{\text{blood}}\) is the specific heat of blood, and \(u_a\) denotes the arterial core blood temperature. The laser source term, \(q_{\text{laser}}\), is modelled using a standard diffusion approximation \([65]\). Power is denoted \(P\), the volume of applicator is denoted \(U_{\text{tip}}\), and the volume of the biological domain is denoted \(U\). Optical parameters include the absorption, scattering, and anisotropy factor, denoted \(\mu_a\), \(\mu_s\), and \(g\), respectively. Arrhenius damage model, \(\Omega\), parameters are denoted, \(A\), \(E_A\), and \(R\). The objective of this work is to use this mathematical model to predict the 4D temperature field, \(u\), as a function of a random vector, \(\vec{Z}\), with a known probability distribution that mathematically represents our uncertainty the optical parameters, perfusion, and conduction, \(\vec{Z} \equiv (Z_k, Z_{\omega_{\text{native}}}, Z_{\omega_{\text{coag}}}, Z_g, Z_{\mu_{a_{\text{native}}}}, Z_{\mu_{a_{\text{coag}}}}, Z_{\mu_{s_{\text{native}}}}, Z_{\mu_{s_{\text{coag}}}})\).

Statistical methods provided by uncertainty quantification techniques such as generalised polynomial chaos provide novel methodologies for modelling the complex bioheat transfer phenomena. In particular, it is well known that the constitutive parameters behave non-linearly with temperature increase and tissue damage. Constitutive parameters that account for damage-dependent non-linearities of the perfusion, thermal conductivity, and optical parameters \([177]\) are generally more scarce than the linear counterparts and the variability of the mathematical form of the constitutive nonlinearities seen within the
literature suggests a potentially higher degree of uncertainty within the non-linear parameters [4, 62, 147, 178, 179]. Here we will consider the uncertainty associated with both linear and non-linear constitutive forms of the perfusion, absorption, and scattering. A goal of our work is to investigate if a relatively simple linear model with physically meaningful bounds on constitutive values can be coupled with stochastic methods to produce useful predictions. Stochastic parameters associated with linear forms of the BHTE are chosen by the following expressions that are spatially homogenous and constant in time.

\[ k(\vec{Z}) = Z_k \quad \omega(\vec{Z}) = Z_{\omega_{\text{native}}} \quad g(\vec{Z}) = Z_g \]

\[ \mu_a(\vec{Z}) = Z_{\mu_a^{\text{native}}} \quad \mu_s(\vec{Z}) = Z_{\mu_s^{\text{native}}} \]

While several empirical models of non-linearities are available, for feasibility, a common form of the constitutive non-linearities (Equation 3.3) was considered for absorption, scattering, and perfusion as a function of Arrhenius thermal damage, \( \Omega \). As seen in Figure 3.1, for this particular analytical form chosen [62], undamaged constitutive values transition to coagulated values between the temperature range of 51–61 °C. Similar to previous studies [140] of the time-temperature histories relevant to MRgLITT, the tissue is fully damaged at a threshold of approximately 61 °C.

\[ \mu_a(\vec{Z}) = Z_{\mu_a^{\text{native}}} + \frac{\Omega}{\ln 2 + \Omega} (Z_{\mu_a^{\text{coag}}} - Z_{\mu_a^{\text{native}}}) \]

\[ \mu_s(\vec{Z}) = Z_{\mu_s^{\text{native}}} + \frac{\Omega}{\ln 2 + \Omega} (Z_{\mu_s^{\text{coag}}} - Z_{\mu_s^{\text{native}}}) \]

\[ \omega(\vec{Z}) = Z_{\omega_{\text{native}}} + \frac{\Omega}{\ln 2 + \Omega} (Z_{\omega^{\text{coag}}} - Z_{\omega_{\text{native}}}) \]

The native conduction, \( Z_k \), perfusion, \( Z_{\omega_{\text{native}}} \), optical scattering, \( Z_{\mu_s^{\text{native}}} \), optical absorption, \( Z_{\mu_a^{\text{native}}} \), and the optical anisotropy, \( Z_g \), as well as the coagulated values of the absorption, \( Z_{\mu_a^{\text{coag}}} \), scattering, \( Z_{\mu_s^{\text{coag}}} \), and perfusion, \( Z_{\omega^{\text{coag}}} \), are understood mathematically as uniform random variables with quantitative bounds given in Table 3.1. As seen in Figure 3.1, the uncertainty range of constitutive non-linearities is considered as a subset of the uncertainty within the linear UQ problem.
Figure 3.1: A graphical illustration of the non-linear constitutive model [62] used for the perfusion and optical absorption is shown. The scattering behaves similar to the absorption. Damage, perfusion, and absorption are plotted as a function of a time-temperature history representative of those observed in MRgLITT procedures. As shown, the native undamaged constitutive values transition into coagulated constitutive values between temperatures of approximately 51°C–61°C. Similar to previous results [140], the tissue is fully damaged at a threshold of 61°C.
Table 3.1: Literature-based constitutive values [79, 80, 177, 180–186]. A table of the constitutive values used for perfusion, conduction, absorption, and scattering is shown. Uniform distributions are denoted \( U(a, b) \). Deterministic values are otherwise used. Values for density, specific heat, and Arrhenius parameters are as follows: \( \rho = 1045 \) (kg/m\(^3\)), \( c_{\text{blood}} = 3840 \) (J/kg/K), \( c_p = 3600 \) (J/kg/K), \( A = 3.1\text{E}98 \) (s), \( E_A = 6.28\text{E}5 \) (J/mol), \( R = 8.314 \) (J/mol/K).

<table>
<thead>
<tr>
<th>Figure</th>
<th>( \omega ) [kg/(m(^3)s)]</th>
<th>( k ) [W/m K]</th>
<th>( \mu_a ) (1/m)</th>
<th>( \mu_s ) (1/m)</th>
<th>( g ) (Unity)</th>
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<td>2A</td>
<td>( U(3, 9) )</td>
<td>0.527</td>
<td>500</td>
<td>14000</td>
<td>0.88</td>
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<tr>
<td>2A</td>
<td>6</td>
<td>( U(0.490, 0.527) )</td>
<td>500</td>
<td>14000</td>
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<tr>
<td>2A</td>
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<td>0.527</td>
<td>( U(400,600) )</td>
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<tr>
<td>2A</td>
<td>6</td>
<td>0.527</td>
<td>500</td>
<td>( U(11200, 16800) )</td>
<td>0.88</td>
</tr>
<tr>
<td>2A</td>
<td>6</td>
<td>0.527</td>
<td>500</td>
<td>14000</td>
<td>( U(0.88, 0.95) )</td>
</tr>
<tr>
<td>2B</td>
<td>6</td>
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<td>Linear ( U(50, 600) )</td>
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<tr>
<td>2B</td>
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<td>Native ( U(5000, 300000) )</td>
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<td></td>
<td>Coag. ( U(30000, 500000) )</td>
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</table>

Coag., coagulated.
Table 3.1: Literature-based constitutive values [79, 80, 177, 180–186]. A table of the constitutive values used for perfusion, conduction, absorption, and scattering is shown. Uniform distributions are denoted $U(a, b)$. Deterministic values are otherwise used. Values for density, specific heat, and Arrhenius parameters are as follows: \( \rho = 1045 \) (kg/m\(^3\)), \( c_{\text{blood}} = 3840 \) (J/kg/K), \( c_p = 3600 \) (J/kg/K), \( A = 3.1E98 \) (s), \( E_A = 6.28E5 \) (J/mol), \( R = 8.314 \) (J/mol/K).

<table>
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<tr>
<th>Figure</th>
<th>$\omega$ [kg/(m(^3)s)]</th>
<th>$k$ [W/m K]</th>
<th>$\mu_a$ (1/m)</th>
<th>$\mu_s$ (1/m)</th>
<th>$g$ (Unity)</th>
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<td>14000</td>
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</tr>
<tr>
<td>2C</td>
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<td>500</td>
<td>14000</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Coag. $U(0, 3)$</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D</td>
<td>$U(3, 9)$</td>
<td>$U(0.490, 0.527)$</td>
<td>$U(400, 600)$</td>
<td>$U(11200, 16800)$</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.527</td>
<td>$U(4, 200)$</td>
<td>$U(11200, 16800)$</td>
<td>$U(0.85, 0.95)$</td>
</tr>
<tr>
<td>4, 5, 6</td>
<td>6</td>
<td>0.527</td>
<td>$U(400, 600)$</td>
<td>$U(11200, 16800)$</td>
<td>$U(0.85, 0.95)$</td>
</tr>
<tr>
<td>5A (WM)</td>
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<td>320</td>
<td>46900</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Coag., coagulated;

WM, white matter.
3.3.2 Constitutive data

Constitutive parameter values [80,177,180–183,187] used in simulating the bioheat transfer for the \textit{in vivo} brain data and \textit{ex vivo} phantom set-up are provided in Table 3.1. Variability in the model parameters [78,177,183] was input into the gPC model as uniformly distributed random variables using the bounds shown in Table 3.1. The variability in the ranges presented encompasses all conceivable healthy values as well as the extremum of constitutive non-linear dependence on temperature. The values for the Arrhenius dose parameters listed in Table 3.1 are from Henriques and Moritz’s classic work [135]. The choice of dose parameters is dependent on what end point is sought. Here the threshold is tissue death by any heating effects shortly (< 20 min) after treatment. The dose analysis for the four canines, described by Yung et al. [140], demonstrates that an Arrhenius dose module using Henriques’ dose values leads to agreement with post-treatment, post-contrast T1-weighted MRI.

3.3.3 Optical parameter uncertainty

Relatively large variability may be seen in optical parameter values reported in the literature, Table 3.1. These differences may be associated with different techniques for \textit{in vivo} and \textit{in vitro} measurements, different radiative transport models, and differences in preparation of tissue specimens [188,189]. The non-linear behaviour of optical parameters is well known [62,177,190–192] and further increases the uncertainties in optical properties. For example, a 10% increase in the absorption coefficient and a 2–4-fold increase in the scattering coefficient was seen between native and coagulated brain tissue [177,191]. Further, the blood content of the tissue has been seen to affect the optical properties [193]. Significant changes in the optical properties of the blood can be expected with varying concentrations of haematocrit and oxygen concentration. There is also great uncertainty in the tumour type to use for the optical parameter values as well as blood content of the tumour. This
may particularly contribute to the uncertainty in the optical parameters when irradiating heterogeneous tumours where the patient-specific blood content and the amount of cerebral spinal fluid (CSF) present may vary significantly.

Grey matter optical parameter values—$\mu_a$, $\mu_s$, and $g$—were used in simulating MRgLITT in normal canine brain tissue. For non-linear simulations, the values of absorption and scattering were set to represent the native state and transition to a coagulated state (Equation 3.3). The range of optical values used in the linear simulation for comparison against the nonlinear simulation is a superset of the range of the native and coagulated transition, listed in Table 3.1, Figure 3.2(B) and (C).

### 3.3.4 Multiplanar magnetic resonance thermal imaging in phantom and animal models

Simulations were compared to MRTI data obtained from a safety and feasibility study of MRgLITT conducted in the brains of four clinically normal mixed breed hounds (20–25 kg) [65, 140]. MRTI data was also obtained from an MRgLITT heating experiment in a perfusionless *ex vivo* tissue phantom [154] constructed from an excised canine prostate embedded within 1% agar, Figure 3.3. MRTI data was acquired on a 1.5 T MRI scanner (ExciteHD®, GE Healthcare Technologies, Waukesha, WI) with an 8-channel, receive-only phased array head coil (MRI Devices, Gainesville, FL) and a 2D multi-slice 8-shot EPI sequence [194] (flip angle (FA) = 60°, field of view (FOV) = 20 × 20 cm, slice thickness 4 mm, TR/TE = 544/20 ms, encoding matrix of 256 × 128, with 5–6 s per update). The procedures were conducted under institutional protocol. The canines were anaesthetised with ketamine/midazolam (Versed) solution (ketamine, 10 mg/kg; midazolam, 0.5 mg/kg; and glycolpyrrolate, 0.01 mg/kg), incubated, and aspirated with a mixture of 2% isoflurane/oxygen. Once the dogs were anaesthetised, a burr hole was introduced in the right parietal bone of each animal. In each case, the laser applicator was percutaneously placed through the burr hole and into the clinically normal brain. The silica applicator was 400 µm
in diameter with a 1-cm axial length for laser diffusion. The laser wavelength was 980 nm with a maximum power of 15 W (Photex 15, BioTex, Houston, TX). The applicator was water cooled with a maximum flow of 15 ml/min. Power histories are shown in Figures 3.3 and 3.4. Fluorooptic probes were not included to attempt to avoid susceptibility artefact.
Figure 3.2: These plots are spatial profiles that demonstrate the properties of a stochastic BHTE, with inputs listed in Table 3.1. A is a linear sensitivity study; each colour represents data from a univariate model, i.e. one parameter is varied while all others are constant. A has the following plots, listed from low to high variance at peak heating: perfusion (fuchsia), conductivity (green), optical scattering (blue), optical absorption (red), and optical anisotropy (violet). The parameters’ relative sensitivities can be seen in this figure. For example, perfusion is proportionally varied more than the optical absorption and scattering parameters, but the optical parameters still have a greater temperature variance. The BHTE is most sensitive to the anisotropy factor in this study. B and C are a sensitivity study comparing linear and non-linear perfusion parameters; For B and C, the solid lines represent the CDF = 2.3 and 97.7%; the enclosed region is the central 95% confidence interval. B has optical absorption (red and green with dashed lines) and scattering (fuchsia and blue with solid lines) while C has perfusion. The linear cases’ inputs vary the concerned parameter over a range that includes both the native and coagulated states of the non-linear case. The plots demonstrate coagulation affecting the temperature distributions. D simultaneously varies optical scattering, optical absorption, conductivity, and perfusion. The difference between the worst-case scenarios (black) and CDF = 1% and 99% (red) is shown.
3.3.5 Computational methods

A hexahedral finite element mesh that conforms to the geometric details of the water cooled laser applicator [65, 195] was created in CUBIT (Sandia National Laboratories, Albuquerque, NM) [196]. A 21°C Dirichlet boundary condition representing the water-cooled catheter was applied to the domain of the applicator. Simulations at several mesh spatial resolutions were run at quarter symmetry to ensure numerical convergence; 13968/47368/169680 element meshes with 15770/50898/177549 corresponding nodes were evaluated. The DAKOTA software (Sandia National Laboratories) [197] was used to implement the generalised polynomial chaos expansion. Similar to ensuring convergence of the mesh resolution, the number of polynomial chaos basis functions used in the gPC expansion was increased until the truncation error of the gPC expansion was negligible [198]. This was achieved by computing the difference between a lower order and a higher order gPC expansion. When the maximum pointwise difference between a lower order and a higher order gPC expansion was \(< 0.001°C\), the gPC expansion was assumed converged. Using DAKOTA, the gPC expansion order is inferred from the quadrature order in probability space. A quadrature order of four was found to achieve truncation error convergence in the gPC expansion. For comparison to gPC, a worst-case scenario approach was also run [199]. The worst-case scenario approach provides the extreme upper and lower bound of the temperature distribution by considering the extrema of the input parameter variability.
Figure 3.3: The trivariate joint uncertainty of the optical absorption, scattering, anisotropy are input for the gPC simulations. Model parameters are listed in Table 3.1. A is the MRTI of the phantom study at $t = 90$ s. The inner red contour is the $50^\circ$C isotherm for the model’s mean and the outer red contour is for the CDF = 97.3%; CDF = 2.3% never reaches $50^\circ$C. The dark blue contour is the MRTI’s $50^\circ$C isotherm. Only one MRTI isotherm is displayed because the MRTI variance is very small; $\pm 2\sigma$ of MRTI noise is $2^\circ$C. The black rectangles in A, B, and D occlude where the laser fibre was. The superimposed green line represents the location for linear profiles B and D. A green diamond indicates the location of the temporal profile in C. D compares the linear profile of the central 95% confidence intervals of the model and MRTI. In plot D, the model’s mean tracks very well with the MRTI, particularly near the laser fibre ($\pm 6$ mm). D also dramatically shows the potential for non-Gaussian distributions to arise in the temperature model, further illustrated in B. B shows various CDF values tracked in the gPC computer package, DAKOTA. The top red is CDF = 99%, green is the median (50%), red dashed line is the mean, violet is 5%, black is 2.3%, bottom red is 1%. Note the extreme skewness of the model’s temperature output near the fibre, as evidenced by the mean and median being much nearer the higher percentage CDFs than the lower percentage CDFs. The power, displayed as green points, is provided units on the right vertical axis of C.
Figure 3.4: These temporal profiles, A through D, are temporal profiles from canines 1 through 4, respectively. The red and blue dashed and solid lines represent the same mean and CDF values listed in Figure 3.5. The green points represent the power history. The spatial locations of the temporal profiles are shown in Figure 3.6 via the green diamonds. A and D show the best agreement of the four plots. B is more successful at the beginning of the imaging sequence but the model is much colder at later time points. C tends to be somewhat cooler, but significant overlap remains between the MRTI and model distributions.

3.4 Results

A sensitivity study of the thermal conduction, perfusion, absorption, scattering, and anisotropy is presented in Figure 3.2. The sensitivity study was performed by investigating the effect of the uncertainty range of each parameter individually on the resulting temperature field’s standard deviation (Figure 3.2A) or mean and 95% confidence interval (Figure 3.2B-D). Here the 95% confidence intervals are reported as the output cumulative temperature
distribution (CDF) between 2.5% and 97.5%. Representative profiles of the temperature field’s standard deviation resulting from considering the uncertainty in thermal conduction, perfusion, absorption, scattering, and anisotropy individually is shown in Figure 3.2(A). Results in Figure 3.2(A) are shown for the linear heat transfer problem near the maximum heating time point. Given the physically meaningful distributions found in the literature, Table 3.1, the resulting temperature field was found to be least sensitive to the perfusion and most sensitive to the anisotropy. The sensitivities in Figure 3.2(A) can be summarised by listing their peak standard deviations in °C: $g$ 3.51; $\mu_a$ 2.94; $\mu_s$ 1.84; $k$ 1.43; and $\omega$ 0.94.

The sensitivity of the absorption, scattering, and perfusion non-linear parameters on the resulting temperature distribution is shown in Figure 3.2(B) and (C). As seen in Figure 3.1, the uncertainty in the linear problem was assumed to be bound the total nonlinear variations and the resulting linear temperature field bounds the non-linear temperature field, Figure 3.2(B) and (C). The effect of thermal coagulation is seen to shift the means of the output distributions for the non-linear perfusion, absorption, and scattering (not shown). Figure 3.2(D) demonstrates the difference between uncertainty quantification from multivariate generalised polynomial chaos and worst-case scenarios as an estimate for uncertainty quantification.

Of the five univariate gPC expansions considered, the sensitivity of the final temperature distribution 95% confidence interval for the MRgLITT simulations is seen to be least sensitive to conduction and perfusion variability. Subsequent MRgLITT simulations consider the trivariate joint uncertainty of the optical parameters, absorption, scattering and anisotropy, for comparison to MR thermometry data. The thermometry data shown was generated using standard complex phase differencing techniques and SNR-based estimates of the Gaussian uncertainty in the measured temperature value [65].

Figure 3.3 compares the 95% confidence interval of the gPC MRgLITT simulation to MRTI data acquired during an ex vivo heating of canine prostate tissue. The phantom provides a perfusion-less environment to compare theory to experiment. The trivariate joint
uncertainty of the absorption, scattering and anisotropy are input into the gPC simulations. Model parameters used are provided in Table 3.1. Figure 3.3(A) shows a temperature map of the MRTI near a maximum time heating point. A plot of temperature over time comparing measured to predicted values of temperature is shown in Figure 3.3(C). The power history is provided on the right axis. A spatial profile of the experimental and simulation temperature values is shown in Figure 3.3(B) and (D). The location of the spatial profiles and temporal profiles are provided in Figure 3.3(A). During heating, good agreement is seen between the measured and predicted temperature values.

The trivariate joint uncertainty of the absorption, scattering and anisotropy are input into the gPC simulations and compared to MRTI data acquired during four canine MRgLITT experiments. The comparison is provided in Figures 3.4-3.6. MRTI from the four canine MRgLITT procedures is shown in Figure 3.6. Contours of the 60°C isotherm of the MRTI are compared to the 95% confidence interval of the gPC predictions. Locations of spatial and temporal profiles used in Figures 3.4 and 3.5 are shown. An additional simulation varying perfusion only and using optics parameters from white matter is shown to compare the differences in input parameters from white matter to grey matter, Figure 3.5(A). The white matter-based, $\omega$-univariate simulation shown in Figure 3.5(A) is clearly much colder and led to the decision to use grey matter weighted optics parameters in the trivariate simulations, shown in Table 3.1. Spatial and temporal profiles, seen in Figures 3.4 and 3.5, show that canines 1 and 2 had a majority of overlapping regions between the MRTI and the simulations’ 95% confidence intervals. It should be noted that canines 3 and 4’s disagreement occurs relatively distant from the laser fibre.
Figure 3.5: Plots A through D correspond to canines 1 through 4 at the same time points described in Figure 3.6. A also contains a perfusion univariate model that uses optical scattering and absorption from white matter tissue (violet). The black rectangles obfuscate the portions of the linear profiles that are on the laser fibres because those regions provide invalid comparisons. A suggests that white matter optical scattering and absorption parameters produce profoundly colder temperatures. In plots A and B the trivariate model tends to overlap the MRTI well. Plots C and D show some agreement near the fibre (± 3 mm), but diverge at further distances.
Figure 3.6: These images are MRTI from the four canine normal brain MRgLITT ablations. All images are from a slice that intersects the longitudinal axis of the laser applicator. Images A, B, C and D respectively correspond to canines 1, 2, 3 and 4 near maximum heating times $t = 432\, \text{s}$, $222\, \text{s}$, $120\, \text{s}$, and $135\, \text{s}$. The superimposed green lines represent where the linear profiles for the four canines are plotted for Figure 3.5. Green diamonds indicate the location of temporal profiles in canine Figure 3.4. The black rectangles in each image are where the laser fibres were. The concentric red contours correspond to the predicted 60 $^\circ\text{C}$ isotherm contours with probabilities CDF = 2.3% and 97.7%. The areas between the red contours represent the central 95% of the model’s temperature distribution. According to the model, the CDF = 2.3% contour has a high probability of occurring, i.e. 97.7%. The dark blue and light blue contours respectively are the 60 $^\circ\text{C}$ isotherms from the MRTI temperature $\pm 2\sigma$ of MRTI noise.
3.5 Discussion

A generalised polynomial chaos (gPC) method was used to propagate the uncertainty in
the biothermal and optical parameters. A finite element-based stochastic form of the 3D
Pennes bioheat transfer model was implemented for these purposes. The ability to accept
plausible distributions of the biothermal and optical parameters and output realistic distri-
butions of the temperature mean and variance is a novel aspect of gPC-based simulation.
In a probabilistic bioheat simulation the challenge shifts from utilising the most precise
constitutive values to identifying an appropriate input distribution. However, when using
gPC, the model input distributions are limited to the Wiener-Askey scheme [171]. The two
distributions considered were the Gaussian and uniform distributions. Because Gaussian
distributions have been successfully and ubiquitously applied to probabilistic natural phe-
nomena, Gaussian distributions were initially identified as an option. However, Gaussian
distributions are positive from \(-\infty\) to \(+\infty\). In order to be physical, the constitutive values
must be positive. If a Gaussian distribution was applied to the constitutive input distri-
butions, the model would be influenced by non-physical inputs. The uniform distribution
was chosen for use in the constitutive value distributions because it is straightforward to
restrict the distribution to physical values.

The sensitivity study, displayed in Figure 3.2, shows the output variance of the five
univariate models. It is important to note the relative input variance, based on published
literature values, to the output variance. For example, \(\omega\) is varied from 3 kg m\(^{-3}\)s\(^{-1}\) to
9 kg m\(^{-3}\)s\(^{-1}\), i.e. the variance is the mean \(\pm 50\%\). When compared to the variance of \(\mu_a\)
(mean \(\pm 20\%\)), it is evident that the BHTE is much more sensitive to \(\mu_a\) than \(\omega\). Namely,
even though \(\omega\) is proportionally varied more than \(\mu_a\), the output temperature variance due
to \(\omega\) is considerably less than \(\mu_a\). The parameters found to produce the greatest variances
were the optical parameters. Further, for the parameter range considered, the confidence
intervals of temperature simulations using non-linear temperature and damage-dependent
perfusion, scattering, and absorption (Equation 3.3) is bounded by the linear temperature simulations. Within this statistical setting, the linear problem with its associated uncertainty is used as a surrogate for the more complex non-linear bioheat transfer phenomena. The linear form of the optical parameters, $\mu_a$, $\mu_s$, and $g$, were used in the trivariate gPC-based MRgLITT simulations for comparison with the phantom experiments and canine ablations.

Comparison of worst-case scenarios and gPC estimates, Figure 3.2(D), demonstrate that the deterministic worst-case scenarios do not adequately capture the bulk of the statistical information in multivariate simulations, the worst-case scenarios only indicate the extrema. This is particularly true as the joint uncertainty of progressively more parameters is expanded in probability space. It is conceivable that worst-case scenarios could approximate gPC estimates in special cases, for example univariate simulations or parameters with low sensitivity yielding low output variance. However, these same special cases are less likely to require uncertainty quantification, which is the reason we used to legitimise our focus on the optics when comparing the trivariate models for the gPC-based MRgLITT simulations.

A more exhaustive application of uncertainty quantification to LITT would also examine the effect of other bioheat parameters, for example $\rho$, $c_t$, and $\mu_a$, and thermal dose parameters. Uncertainty in the dose parameters (either Arrhenius or cumulative effective minute (CEM) models) [77] depends on the temporal length of the hyperthermia treatment. In the case of relatively temporally short, spatially small $>60\,^\circ\text{C}$ ablations, thermal dose models predict the spatial transition between coagulative necrosis of tissue and survival is small. However, for sub-ablative hyperthermia where thermal dose is accumulated over greater time, variance in thermal dose parameters may lead to appreciable spatial variance in the lethal threshold region or other interesting thermal dose levels. Future studies should investigate uncertainty in thermal dose parameters’ effect on thermal dose uncertainty, especially for temporally longer hyperthermia treatments.
Regarding the MRTI for canine 1, Figures 3.4-3.6, it should be noted that the canine’s brain ventricle was punctured by the catheter. The ventricle leaked cerebral spinal fluid (CSF) into the catheter’s insertion tract and ultimately pooled near one side of the laser fibre. The effect of the CSF on the thermal ablation can be seen as reduced temperature for the lower side of the thermal lesion in Figure 3.1. The effect is most obvious in the MRTI’s 60°C isotherms. The model did not account for the presence of the CSF and therefore the regions affected by the CSF were excluded from analysis. Regarding the MRTI in general, the pixels imaging the laser fibre and very proximal regions affected by susceptibility artefact were not included in the linear profiles or isotherm contours. Further sources of discrepancy between simulation and MRTI during the cooling regime, Figures 3.3(C) and 3.4, are not seen in studies with external optical fibres [200] and are likely due to inaccuracies of the Dirichlet boundary condition to model the convective cooling of the catheter. Validation of physics-based models [57,201] of the convective heat transfer of the cooling fluid through the laser applicator is a topic of future work.

Despite multivariate gPC expansions being more appropriate for thermal therapy simulation, univariate gPC expansions may be used in future investigations to identify which parameters create the greatest variance of the temperature output, and subsequently restrict the gPC expansion to parameters that affect the temperature output the greatest. Improving the input distributions for the constitutive values should be investigated. Ideally, the model’s constitutive distributions would reflect the natural distributions of the constitutive parameters. The Wiener-Askey scheme includes gamma and beta distributions that are each a set of parameterised distributions. Both gamma and beta distributions include distributions that are not negative and resemble the Gaussian distribution’s distinctive ‘bell curve’. While Gaussian-like distributions exist, there is presently no particular reason any single distribution should work best. It may be sufficient to attempt an array of distributions in order to discover distributions that minimise the difference between the model and MRTI. Future investigations should additionally explore further statistical metrics of
the model’s outcome. Possible tests include using spatio-temporal pixel-wise statistical
tests for the difference or similarity between the model’s mean and MRTI’s temperature.
The common example test for the difference of means is the Student’s $t$-test, however, the
model’s polynomial expansion is not generally a Gaussian distribution so other tests should
be sought.

This investigation took the natural step of comparing the model’s confidence interval
to the MRTI’s confidence interval. In the case of gPC, the polynomial expansion probability
distribution function was integrated to yield the polynomial expansion’s CDF. The CDF
in turn indicated the probability of a threshold temperature (e.g. the temperature is >
60 °C) as a function of distance from the laser fibre. These probabilities have a clear use
in planning for thermal ablations. A stochastic simulation with temperature UQ gives
the surgeon a probabilistic measure of the temperature. There are at least two methods
of clinically using temperature UQ. First, the physician can plan the ablation using the
stochastic model’s mean temperature prediction and the variance about the mean. For
example, if a physician observes a large variance about the mean, the simulation cannot be
implicitly trusted. Alternatively, temperature UQ could aid ablation planning by displaying
an isotherm that is very likely to occur. For example, the physician could plan the ablation
based on the CDF = 5% level. That is, the model would display a treated region that has
a 95% chance of occurring. While deterministic thermal predictions do not have a measure
of their uncertainty, a stochastic simulation provides confidence intervals. An example
would be a surface contour that demarcates a volume that has at least a 95% probability
of reaching 60 °C. Uncertainty quantification to create a ‘high probability of treatment’
contour is a highly desired goal. An accurate, high probability of treatment contour would
allow physicians to quantify a measure of the probability of success. Also, there is little risk
of overtreatment if the contour exceeds the desired treatment region; MRgLITT’s real-time
MRTI provides the physician with feedback for ceasing treatment.

In conclusion, results demonstrate the utility of generalised polynomial chaos (gPC)
expansion techniques to propagate parameter uncertainties through the computer model of bioheat transfer, and quantify uncertainties in the resulting output temperature distributions. Given parameter uncertainties and mathematical modelling approximations of the Pennes bioheat model, the 95% confidence intervals within the statistical framework demonstrate conservative estimates of the thermal therapy outcome and have potential for use as a computational prediction tool for thermal treatment planning.

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Declaration of interest

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Chapter 4

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

This Chapter is a near-verbatim quotation of Fahrenholtz et al. [67]. Among the specific aims, this Chapter is the calibration and simulated validation of the finite element method model. The Chapter uses English grammar and spelling of the United Kingdom. The only intended modifications are the numbering of citations, equation numbers, figure numbers, table numbers, and section numbers. The citations are numbered according to the dissertation, as opposed to the quoted journal article. Its citation, according to the Taylor & Francis online-only format, is thus:


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4.1 Abstract

A cross-validation analysis evaluating computer model prediction accuracy for a pri-
ori planning magnetic resonance-guided laser-induced thermal therapy (MRgLITT) pro-
ducts in treating focal diseased brain tissue is presented. Two mathematical models are
considered. (1) A spectral element discretisation 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 superpo-
sition of analytic point source heating functions is also considered. Prediction accuracy is
retrospectively evaluated via leave-one-out cross-validation (LOOCV). Modelling predic-
tions 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 are 0.7323 and 0.8001 respectively, with 15 of 22 DSC values exceeding the success
criterion of \( \text{DSC} \geq 0.7 \). The steady-state model’s DSC mean and median are 0.6431 and
0.6770 respectively, with 10 of 22 passing. A one-sample, one-sided Wilcoxon signed-rank
test indicates that the transient finite element method model achieves the prediction success
criteria, \( \text{DSC} \geq 0.7 \), at a statistically significant level.

4.2 Introduction

Approximately 211 000 patients in the USA present each year with brain tumours. Of these,
38 000 are benign primary tumours, 23 000 malignant primary tumours, and 150
000 are metastatic, originating largely from lung, breast, and melanoma \([35,205–208]\). 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 2.5–3.0 cm in which the size or location of the tumour 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 tumours, tumours under 2.5 cm in diameter, and deep seated tumours [209]. An additional target in the brain is epileptogenic foci for patients with medically refractory epilepsy, where MRgLITT is being considered for the surgical armamentarium for those patients [37,43]. 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 [55, 108,109, 142,143,210,211].

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 [15,148,212,213] as well as to estimate the extent of tissue damage [78,214,215]. However, the heating induced by the laser is not constrained exclusively to tumour 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 co-morbidity of intervening or adjacent tissue. Surgical workflows in which the operating room and MRI suite are separate [37,39] escalate the advantages of a predictive model.

This manuscript focuses on the development of a practical methodology for evalu-
ating 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 [216, 217]. Here we assume that a Pennes bioheat transfer model [160] 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 summarise the high dimensional thermometry dataset with a low dimensional model parameter subset.

Two distinct modelling approaches are pursued: 1) A GPU implementation of an unstructured hexahedral spectral element method for predicting the bioheat transfer is developed, and 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 modelling approaches presented provide an environment to critically evaluate model accuracy and selection for therapy planning of MRgLITT. Both approaches build intuition into 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 [218–222].

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4.3 Methods

4.3.1 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 artefacts, low signal-to-noise, and catheter-induced signal voids that spuriously reduce the modelling accuracy. Each patient was treated with the Visualase Thermal Therapy System (Visualase, Houston, TX). The Visualase\textsuperscript{®} 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 \( \mu \)m core silica fibre optic with a cylindrical diffusing tip housed within a 1.65 mm diameter saline-cooled polycarbonate cooling catheter \([109, 215]\); see Figure 4.1. Applicator cooling lines and laser fibre optics are connected through a waveguide between the control room and the bore of the MR magnet. An MR-compatible head holder is used to secure the patient’s head. The trajectory to the targeted tumour lesion was obtained using the Brainlab navigation system (Brainlab, Westchester, IL). 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\textsuperscript{®} 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 \([223]\) (flip angle = 30°, field of view = 24 \( \times \) 24 cm\(^2\), matrix size = 256 \( \times \) 128, repetition time/echo time = 37.5/20 ms, receive-only head coil, 5 s per update). The imaging plane was chosen perpendicular to the axial direction of the applicator and allowed monitoring of critical structure regions. The Visualase\textsuperscript{®} 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) [129]. The total temperature change, $\Delta u$, is proportional to the measured phase change, $\delta \phi$.

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

Here $\alpha$ is the temperature sensitivity coefficient, $\gamma$ 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 $u_0 = 37.0^\circ C$ is assumed to obtain absolute temperature. An Arrhenius rate process model [224] was used to evaluate the thermal dose resulting from the timeâ€“temperature history of the laser exposure.

$$
\Omega(t) = \int_0^t Ae^{-\frac{E_A}{RT_\tau}} d\tau
$$

(4.1)

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 3.1E98 s$^{-1}$ and 6.28E5 (J/mol), respectively, and have been used in previous studies [61, 142, 145]. $R$ is the universal gas constant. The thermal dose was assumed to be lethal at doses $\Omega \geq 1$ as seen in previous reports [142,145].

Prior to treatment delivery, a low power test pulse — e.g., 4 W for 30 s — is applied to verify the position of the diffusion fibre optic within the catheter. The test pulse is sufficient to allow thermal visualisation 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 4.1. All DICOM header information was imported into an SQLite database to provide efficient queries and organise thermometry data for reproducible analysis and processing. The schema provided by the Slicer [225] DICOM module was used as a 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, for example. Metadata needed for the analysis included the following.

1. The applicator orientation and heating region of interest (ROI) were manually identified within the imaging datasets for input into the computer models discussed in the sections immediately below.

2. A text file containing the relevant laser power history for each imaging dataset was parsed and input into the simulation. The power history provides information on the heating and cooling time intervals during the procedure.

4.3.2 Simulation of bioheat transfer within laser irradiated tissue

A time-dependent Pennes [160] bioheat transfer equation provides a computer model for predicting the temperature field resulting from the laser tissue interaction.

\[
\partial u_t - \nabla \cdot (\alpha \nabla u) + \frac{\omega c_{\text{blood}}}{\rho c_p} (u - u_a) = \frac{1}{\rho c_p} q_{\text{laser}} \quad \text{in} \ U \setminus U_{\text{tip}} \tag{4.2}
\]

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

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

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

Here the tissue specific heat, \( c_p \); tissue density, \( \rho \); thermal conductivity, \( k \); perfusion, \( \omega \); blood specific heat, \( c_{\text{blood}} \); and arterial blood temperature, \( u_a \), are deterministic model parameters obtained from the literature [183,226,227], see Table 4.1. The laser source, \( q_{\text{laser}} \), is a deterministic function of the applied power, \( p(t) \); optical scattering, \( \mu_s \); optical absorption, \( \mu_a \); anisotropy factor, \( g \); and distance, \( \|x - \xi\| \), from the source, \( U_{\text{tip}} \). Active cooling of the water flowing through the applicator is modelled 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 4.1.

<table>
<thead>
<tr>
<th>$k$ [$\text{W m K}^{-1}$]</th>
<th>$\omega$ [$\text{kg m s}^{-3}$]</th>
<th>$g$ [Unity]</th>
<th>$\mu_s$ [cm$^{-1}$]</th>
<th>$\mu_a$ [cm$^{-1}$]</th>
<th>$\rho$ [$\text{kg m}^{-3}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.527</td>
<td>9.0</td>
<td>0.88</td>
<td>14000</td>
<td>500</td>
<td>1045</td>
</tr>
<tr>
<td>$c_{\text{blood}}$ [$\text{J kg K}^{-1}$]</td>
<td>$c_p$ [$\text{J kg K}^{-1}$]</td>
<td>$h$ [$\text{W K m}^{-2}$]</td>
<td>$u_{cooling}$ [$^\circ\text{C}$]</td>
<td>$u_a$ [$^\circ\text{C}$]</td>
<td></td>
</tr>
<tr>
<td>3840</td>
<td>3600</td>
<td>100</td>
<td>21</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

An implicit Euler time discretisation is used to reduce the time-dependent bioheat equation, Equation (4.2), into a sequence of elliptical problems. Hexahedral Lagrange elements (polynomial order = 3) were used in the finite element discretisation 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 in the discretisation. 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 minimises the storage requirements and data movement of the finite element elliptical 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 discretisations 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 [228].

All computations were performed on the template hexahedral mesh shown in Figure 4.1(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 discretisation 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 fibre during heating were considered through the boundary conditions at the surface nodes. Similar to previous studies [65], multiple mesh resolutions were considered to ensure convergence of the discretised 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.

4.3.3 Analytic steady state solution

A steady-state version of the Pennes bioheat equation, Equation (4.2), 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 one-dimensional spherically symmetrical radial decomposition of the solution, \( u(r) - u_a = \frac{R(r)}{r} \), simplifies the analysis of the differential operator in spherical coordinates.

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

\[
\left. \frac{du}{dr} \right|_{r_2} = 0 \quad r_1 < r_2
\]

From classical theory [229], the general solution is the linear combination of the homogeneous solution, \( u_h \), and a particular solution, \( u_p = \frac{A}{r} \left( A \exp(-\mu_{\text{eff}} r) + B \exp(-\mu_{\text{eff}} r) \right) \).

From classical theory [229], the general solution is the linear combination of the homogeneous solution, \( u_h \), and a particular solution, \( u_p = \frac{A}{r} \left( A \exp(-\mu_{\text{eff}} r) + B \exp(-\mu_{\text{eff}} r) \right) \).

In this case, the particular solution was obtained from the method of undetermined
coefficients for $A, B \in \mathbb{R}$.

$$u = C_1 \exp \left( \frac{\omega_{\text{blood}}}{k} \frac{r}{r} \right) + C_2 \exp \left( -\frac{\omega_{\text{blood}}}{k} \frac{r}{r} \right) + \frac{\mu_{\text{eff}}^2 P \exp \left( -\mu_{\text{eff}} r \right)}{4 \pi r \left( \omega_{\text{blood}} - k \mu_{\text{eff}}^2 \right)} + u_a \quad (4.3)$$

The boundary conditions are used to determine the coefficients of the homogeneous solution. Applicator cooling is specified by the boundary condition at $r = r_1 = 0.75 \text{ mm}$. The domain is assumed large enough that no heat flux is observed at the far boundary, $r = r_2 = 1 \text{ m}$.

$$\left[ \begin{array}{c} \frac{\exp \left( \frac{\omega_{\text{blood}}}{k} \frac{r_1}{r} \right)}{\frac{\exp \left( \frac{\omega_{\text{blood}}}{k} \frac{r_1}{r} \right)}{\frac{d}{dr} \frac{\exp \left( -\frac{\omega_{\text{blood}}}{k} \frac{r}{r} \right)}{d/r}} r_2} \end{array} \right]$$

The one-dimensional 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 Giordano et al. [230–232]. Heating caused by the cylindrical geometry of the diffusing tip was modelled as evenly distributed point sources, $M = 10$, along the axial dimension of the applicator at positions $r_0_i$.

$$u = \sum_{i=1}^{M} u_h(r - r_0_i) + u_p(r - r_0_i) \quad (4.4)$$

### 4.3.4 Model calibration

For each thermometry dataset discussed above, an inverse problem was solved to calibrate both computer models considered for the heating observed. Previous work [59] showed that the optical parameters provided the highest sensitivity in the temperature predictions over
the range of physically meaningful model parameters. Consequently, optical parameters were considered in the optimisation. 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, $\mu_{\text{eff}}$. At the end of optimisation for one MRTI dataset, the dataset has a corresponding optimal $\mu_{\text{eff}}$ that is constant in space and time.

The out-of-plane translation component, $z$, of the mesh template shown in Figure 4.1 was also optimised. 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, Albuquerque, NM) [197] library was used to optimise $\mu_{\text{eff}}$ for the transient and steady-state models. The $L_2$ error over space and time was used as the objective function.

$$ (\mu_{\text{calib}}, z_{\text{calib}}) = \arg \min_{(\mu_{\text{eff}}, z)} \sum_{k=1}^{N_{\text{step}}} \| u(t_k) - u^{\text{MRTI}}(t_k) \|_2 $$

Thermometry data is denoted $u^{\text{MRTI}}$. All time steps were considered for the transient analysis of the computer model presented above. For the steady-state model presented above, the objective function was the $L_2$ norm between the model and the MRTI’s maximum heating time point. A quasi-Newton optimisation method, opp_q_newton, was implemented as the optimisation algorithm for both models. Gradients of the objective functions were computed using numerical finite differences. The calibration was solved as a bound constrained optimisation problem. A physically feasible parameter bound on the optimisation of the optical parameters, $\mu_{\text{eff}} \in [0.8, 400] \text{ m}^{-1}$, was obtained from the literature [227]. During calibration, the initial value for $\mu_{\text{eff}}$ was 180 m$^{-1}$. The initial value was calculated via the $\mu_{\text{eff}}$ identity from Equation (4.2) and the $\mu_a$, $\mu_s$, and $g$ values from Table 4.1. The slice thickness of the MR thermometry data was used to bound the optimisation of the
4.3.5 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 [218–222]. 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 tumour 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 the previous section. The LOOCV algorithm is executed as:

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

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

- Tissue damage on the $i$-th dataset is predicted by using the average, $\mu_{\text{eff}}^i$, 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.

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

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 (4.1), 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 $57^\circ$C isotherm produced damage regions similar to the Arrhenius model for the ablation regime considered in this study [140].

The trained model’s predictive ability is evaluated by analysing the distribution of DSC values from the $N$ iterations of LOOCV. A one-sample, one-sided Wilcoxon signed-rank test examines whether the trained model prediction’s median exceeds $\text{DSC} \geq 0.7$. One-sample calculations were computed using a threshold DSC value, 0.7, as the null hypothesis $H_0$.

\[ H_0 : \text{DSC} = 0.7 \quad H_1 : \text{DSC} > 0.7 \]

The value chosen is a commonly accepted value in image processing literature [9, 140, 233]; $\text{DSC} = 1$ implies complete agreement between the measure and predicted damage model, i.e. the predicted and measured damage volumes completely overlap. A two-sample, paired Wilcoxon signed-rank test was used to compare whether the two models’ prediction medians were statistically different from one another. All statistical tests and descriptive statistics were evaluated on GraphPad Prism 6.01 (GraphPad Software, La Jolla, CA).
Figure 4.1: (A) The Visualase® applicator modelled 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 is shown of the thermometry data at two points within the brain tissue, \(\sim 1\) mm from the applicator. The corresponding power history is also shown.
Figure 4.2: Representative thermometry data and calibrated model damage predictions. (A) The magnitude of the complex valued thermometry data provides a visualisation 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 $3.75 \times 3.28$ cm$^2$ field of view and is shown in (B)–(D). (B) MR thermometry at maximum heating is shown. (C) finite element method (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 $57^\circ$C isotherm. The colour map indicates the geometrical overlap used in DSC calculations; the legend is at right (C). Respective DSC values for the FEM model (C) and steady-state model (D) are DSC = 0.8385 and DSC = 0.7442.

Figure 4.3: 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, $\mu_{\text{eff}}$, recovered from each thermometry dataset considered are shown. For each calibration the bound constrained optimisation was restricted to a range obtained from literature, $\mu_{\text{eff}} \in [0.8, 400]$ m$^{-1}$. Leave-one-out cross-validation was performed using these 22 $\mu_{\text{eff}}$ values. The nominal value in brain tissue obtained from Welch and van Gemert [39] is $\mu_{\text{eff}} = 180$ m$^{-1}$.
Table 4.2: The descriptive statistics for $\mu_{\text{eff}}$ during optimisation and DSC performance during optimisation and LOOCV ($N = 22$). The transient solve of the Pennes bioheat equation using the Arrhenius damage, Equation 1, is denoted by FEM. Steady-state analysis using the 57°C isotherm damage model is denoted SS. 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.

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

Representative thermometry images and calibrated computer model predictions are shown in Figure 4.2. The measured and predicted thermal dose is displayed. The Arrhenius damage model is shown for the transient model predictions, Equation (4.2), and the thermometry data. The 57°C isotherm damage model is shown for the steady-state analysis, Equation (4.4). Significant variability is seen in the heating due to local patient tissue heterogeneities, tumour location, and nearby heat sinks in the brain such as large blood vessels and cerebral spinal fluid (CSF). This is reflected by the nonellipsoidal 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. Dice similarity coefficient (DSC) ≥ 0.7 [233], between the measured and predicted tissue damage in multiple patients.

The calibration process applied to each thermometry dataset provides a histogram of \( \mu_{\text{eff}} \) values in which the optimal agreement between the model’s prediction and the MR thermometry is observed for each model. The histogram of the \( \mu_{\text{eff}} \) values for both the transient and steady-state model calibrations is shown in Figure 4.3. Literature values of the expected optical properties are provided as a reference. Extrema of the feasible set are obtained from the range of values observed in the literature. Descriptive statistics of the optimised \( \mu_{\text{eff}} \) values, DSC during optimisation, and DSC during LOOCV for both models is provided in Table 4.2; meanwhile, percentiles corresponding to interesting DSC thresholds are presented in Table 4.3.

The overall DSC performance from both models during LOOCV analysis is provided in Figure 4.4. The performance is summarised 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.
Table 4.3: The percentiles that correspond to several interesting DSC thresholds. The ‘opt.’ and ‘LOOCV’ columns refer to the same groups of datasets described in Table 4.2, as well as the datasets plotted in Figure 4.4. 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.

<table>
<thead>
<tr>
<th>DSC threshold (Unity)</th>
<th>FEM (%-ile)</th>
<th>SS DSC opt. (%-ile)</th>
<th>FEM (%-ile)</th>
<th>SS DSC LOOCV (%-ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0</td>
<td>8.357</td>
<td>5.776</td>
<td>7.176</td>
</tr>
<tr>
<td>0.5</td>
<td>2.996</td>
<td>13.34</td>
<td>6.652</td>
<td>14.06</td>
</tr>
<tr>
<td>0.6</td>
<td>11.36</td>
<td>27.34</td>
<td>12.97</td>
<td>27.52</td>
</tr>
<tr>
<td>0.7</td>
<td>15.25</td>
<td>57.64</td>
<td>30.35</td>
<td>58.61</td>
</tr>
<tr>
<td>0.75</td>
<td>30.53</td>
<td>83.22</td>
<td>41.36</td>
<td>85.11</td>
</tr>
<tr>
<td>0.8</td>
<td>44.36</td>
<td>95.12</td>
<td>49.97</td>
<td>96.14</td>
</tr>
<tr>
<td>0.85</td>
<td>67.19</td>
<td>100</td>
<td>82.06</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 4.4: Here, the overall predictive performance, measured by DSC, is displayed for both models. (A) Left is the performance during optimisation, and (B) the right is during LOOCV. 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.

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 \( \geq 0.7 \) at a 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 \( \geq 0.7 \) at a statistically significant level.

4.5 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. Modelling goals are to ultimately utilise the calibrated model in optimising 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 optimised to have DSC \( \geq 0.7 \), both models perform very well. This is because the calibrated \( \mu_{\text{eff}} \) values have a much tighter distribution; i.e. datasets with an optimal DSC \( \geq 0.7 \) had similar \( \mu_{\text{eff}} \) values. Given this investigation is framed as a prediction on the \( N + 1 \) patient, cherry-picking the successful optimisations is inappropriate. Indeed, optimisation results with DSC < 0.7 are included in the LOOCV analysis as seen in the descriptive statistics, Table 4.2. However, it is worth realising that successful optimisations have similar \( \mu_{\text{eff}} \) values and perhaps information beyond the thermometry data would allow the calibration to be grouped into similar cohorts. For example additional meta information on the primary disease type, tumour 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 provide 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 \( \geq 0.7 \). As a quantitative reference, the forward solve mapping between model parameters, Table 4.1, and temperature field is considered the fundamental computational operation of this study. Total run times in the analysis are proportional to the total
number of forward solve iterations in the optimisation and LOOCV analysis. The run times for the forward solves in this study averaged $1.87\times10^2$ s and $1.12\times10^1$ 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 Gflops) workstation with attach GPU accelerators (NVIDIA Tesla M2070 double precision peak 515 Gflops) available to this study. The finite element discretisation 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 maximise floating point operation throughput and minimises 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× speed up over the matrix explicit methods [228,234,235]. Meanwhile, the steady-state superposition analysis, Equation (4.4), provides treatment predictions with fewer floating point operations and would be selected under Occam’s razor [236] 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 [237,238].

The finite element discretisation 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 [239]. As seen in Figure 4.3, 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 modelling 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 [62,63]. 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 characterising the tissue properties.

The finite element discretisation 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 have been shown to provide highly accurate predictions [240–242]. 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 optimise in the higher dimensional parameter space. Tissue heterogeneities could similarly be incorporated into the steady-state superposition analysis, Equation (4.4), 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 [243, 244] framework may be appropriate in which the model parameters recovered may be interpreted as hyper-parameters for the covariance kernels. Similar to physics-based model calibration, optimisation of the hyper-parameters 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 [245] require high resolution FLAIR, T2, and T1 imaging with and without contrast. The SQL database used in organising all data was vital to the reproducibility of the analysis in these efforts; this additional information must be incorporated. Tools for communicating with the neuronavigation software to locate the fibre would also provide further information to improve the analysis throughput and reproducibility. Passive tracking of the applicator location using fiducials placed on the fibre would additionally provide the registration information needed to align the computational domain of the mathematical model.

4.6 Conclusion

Currently, the neurosurgeon reviews anatomical MR images to plan his/her trajectory to reach the tumour with neuronavigation software, but does not have the capability to visualise 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 visualisation and optimisation 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.
Acknowledgments

The authors would like to thank Roger McNichols, PhD, for his assistance in clinical laser ablation as well as the DAKOTA [197], ITK [202], Paraview [203], and CUBIT [196] communities for providing enabling software for scientific computation and visualisation.

Declaration of Interest

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Chapter 5

A global search-based optimization and prediction paradigm for laser ablation

5.1 Introduction

This chapter is an exploration of using the closed-form, analytic steady state model (SSM) of Section 4.3.3 in the logical extreme. In order to orient the reader, this Chapter is the calibration and validation of the SSM — i.e., Specific Aims 2 and 3 for the SSM. Chapter 4 is the calibration and validation of the FEM model. The time-independent SSM represents a surrogate model for the transient FEM model. While this Chapter represents a comparison between the two trained models, it is important to understand that the goal here is not demonstrate the primacy of a particular model. Rather, the Chapter’s purpose is twofold. First, the results of this Chapter demonstrate the trained SSM is an improvement over a naïve SSM. Secondly, the SSM’s performance should be a surrogate for the FEM model.

The SSM’s key strength is its speed engendered by its simplicity. In Chapter 4, the SSM was implemented within a central processing unit (CPU) architecture. The time to run one forward solve was 11.21 s; a gradient-based optimization for one MRTI dataset was 5 min to 10 min. The optimization space was $\mu_{\text{eff}} \in [0.8, 400] \text{ m}^{-1}$. In this chapter, the SSM is implemented within a graphics processing unit (GPU)-accelerated architecture,
yielding prodigiously fast runtimes. The consequence of pairing the SSM with GPUs is the ability to intensively sample the parameter optimization space. The general method of Chapter 5 is similar to Chapter 4. The premise is to use a train-and-predict scheme where an inverse problem trains a model to fit MRTI data from patients.

5.2 Methods

In this chapter, the $N = 22$ cohort of data is the same as from Chapter 4; the difference is found in the improvement of the steady state model (SSM) via graphics processing unit (GPU)-accelerated simulation. The inverse problem is described first. Following the exposition of the inverse problem, the components of the inverse problem are expounded.

5.2.1 Inverse problem

Broadly speaking, an inverse problem brings a simulation into agreement with physical reality by varying the simulation’s input parameters. An inverse problem requires four components:

1. **Gold standard measure of physical reality**
   
   A gold standard measurement of physical reality provides a goal for the simulation to fit. In this Chapter, the gold standard physical measurement is the MRTI-based Arrhenius dose using Henriques and Moritz' parameters [135]. The selection of MRTI datasets is the same $N = 22$ cohort from Chapter 4.

2. **Model**
   
   A model for the prediction of physical reality is the second component. In this Chapter, the model is expressed in Equations (5.4), (5.5), and (5.6) — which are derived from the Pennes bioheat transfer equation [160]. The model is discussed in Section 5.2.3.
3. Objective function

An objective function that can be minimized subsequently brings the model into agreement with physical reality. In this Chapter, the Dice similarity coefficient (DSC) is the primary objective function. Other objective functions are tracked and are discussed in Section 5.2.4.

4. Optimization algorithm

An optimization algorithm that guides the selection of simulation parameters. In this Chapter, the optimization algorithm is a nested global search, as discussed in Section 5.2.5.

5.2.2 Patient datasets

The description of the thermometry datasets is very accurately and concisely detailed in Section 4.3.1. Again, this Chapter and Chapter 4 use the same cohort of $N = 22$ thermometry datasets.

As this document is a dissertation, however, there is a greater availability of space to scrutinize the thermometry datasets — this is continued in Appendix C.

5.2.3 Description of the steady state model

The steady state model (SSM) is the biothermal simulation kernel used within this entire chapter. The analytic derivation and computational implementation are described here.

*Analytic derivation*

This subsection is a recapitulation of Sections 4.3.2 and 4.3.3, with $u_{cooling}$ of Section 4.3.2 being substituted with $u_0$ here. The governing equations for LITT are derived from Pennes
bioheat equation coupled with a source term provided by laser tissue interaction.

\[
\partial u_t - \nabla \cdot (\alpha \nabla u) + \frac{\omega_{\text{blood}}}{\rho_c p} (u - u_a) = \frac{1}{\rho_c p} q_{\text{laser}} \quad \text{in } U \setminus U_{\text{tip}} \quad (5.1)
\]

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

\[
\alpha = \frac{k}{\rho_c p} \quad \mu_{\text{eff}} = \sqrt{3\mu_a \mu_{tr}} \quad \mu_{tr} = \mu_a + \mu_s (1 - g)
\]

\[
n \cdot (\alpha \nabla u) = 0 \quad \text{on } \partial U \quad n \cdot (\alpha \nabla u) = h(u - u_0) \quad \text{on } \partial U_{\text{tip}}
\]

Previous sensitivity analysis have indicated that uncertainty in the optical parameters, \(\omega < k < \mu_{\text{eff}}\), provide the largest affect on the final temperature prediction outcomes \([59]\).

A 1D spherically symmetric radial decomposition simplifies the analysis of the differential operator in spherical coordinates. A particular solution, \(u_p\), will be used to construct a solution.

\[
-\nabla \frac{u_p(r)}{r} + \frac{\omega_{\text{blood}} u_p(r)}{k \mu_{\text{eff}} r} = \frac{1}{k} q_{\text{laser}} \quad \frac{u_p(r)}{r} = \frac{\mu_{\text{eff}}^2 P}{4 \pi r} \exp\left(-\mu_{\text{eff}} \frac{r}{r'}\right)
\]

\[
\frac{d}{dr} \frac{u_p(r)}{r} = \frac{u_p'(r)}{r} - \frac{u_p(r)}{r^2} \quad \nabla \frac{u_p(r)}{r} = \frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{u_p(r)}{r}\right) = \frac{u_p''(r)}{r}
\]
From classical theory \[229\], the general solution is the linear combination of the homogeneous solution, \( u_h \), and a particular solution, \( u_p = \frac{1}{r} \left( A \exp(-\mu_{\text{eff}} r) + B \exp(-\mu_{\text{eff}} r) \right) \). In this case, the particular solution was obtained from the method of undetermined coefficients for \( A, B \in \mathbb{R} \).

\[
\begin{align*}
\frac{\omega_c^{\text{blood}}}{k} r & \left( C_1 \exp \left( \frac{\sqrt{\omega_c^{\text{blood}}}}{k} r \right) + C_2 \exp \left( -\frac{\sqrt{\omega_c^{\text{blood}}}}{k} r \right) \right) + \frac{\mu_{\text{eff}}^2 P \exp(-\mu_{\text{eff}} r)}{4 \pi r \left( \omega_c^{\text{blood}} - k \mu_{\text{eff}}^2 \right)} u_p \Bigg|_{u_p/r} + u_a \quad (5.2)
\end{align*}
\]

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 \( r = r_2 \).

\[
\begin{bmatrix}
\frac{\exp \left( \frac{\sqrt{\omega_c^{\text{blood}}}}{k} r_1 \right)}{r_1} & \frac{\exp \left( -\frac{\sqrt{\omega_c^{\text{blood}}}}{k} r_1 \right)}{r_1} \\
\frac{d \exp \left( \frac{\sqrt{\omega_c^{\text{blood}}}}{k} r \right)}{dr} & \frac{d \exp \left( -\frac{\sqrt{\omega_c^{\text{blood}}}}{k} r \right)}{dr}
\end{bmatrix}
\begin{bmatrix}
C_1 \\
C_2
\end{bmatrix}
= \begin{bmatrix}
\frac{u_0 - u_p(r_1)}{r_1} - u_a \\
- \frac{du_p}{dr} \bigg|_{r_2}
\end{bmatrix}
\quad (5.3)
\]

The 1D solution provides an estimate of the heating at a distance, \( r \), from a single point source. The applicator boundary is at \( r_1 \), and \( r_2 \) is a semi-infinite distance at which the temperature is body temperature, \( u_a \).

Mathematica 7 (Wolfram, Champaign, IL) determined the coefficients of Equation (5.3), which makes an analytic/closed-form expression for temperature, \( u(r) \), in Equation (5.4). Equation (5.4) is relatively long and it is conceivable that certain terms could be effectively approximated. The advantages of approximation include:

1. Simpler implementation into MATLAB-based central processing unit (CPU) and/or CUDA-based GPU computation with reduced risk of introducing errors.
2. Faster computation of the kernel, especially for CUDA-based GPU by reducing the magnitude of data transfer during memory calls.

3. Greater numerical stability in the GPU environment, allowing for a greater range of parameter optimization space to be explored.

However, it was ultimately not necessary to find viable approximations.
\[ u(r) = \frac{u_h(r)}{r} + \frac{u_p(r)}{r} + u_a = \]

\[ u_a + \left\{ \exp \left( -\mu_{eff}(r_1 + r_2 + r) - r \sqrt{\frac{c_{blood} \omega}{k}} \right) \right. \times \]

\[ - \exp \left( \mu_{eff}(r_1 + r) + (2r_1 + r_2) \sqrt{\frac{c_{blood} \omega}{k}} \right) \mu_{eff}^2 P \left( 1 + \mu_{eff} r_2 \right) + \]

\[ \exp \left( \mu_{eff}(r_1 + r) + (r_2 + 2r) \sqrt{\frac{c_{blood} \omega}{k}} \right) \mu_{eff}^2 P \left( 1 + \mu_{eff} r_2 \right) - \]

\[ \exp \left( \mu_{eff}(r_2 + r) + (r_1 + 2r_2) \sqrt{\frac{c_{blood} \omega}{k}} \right) \mu_{eff}^2 P \left( 1 + \mu_{eff} r_2 \right) + \]

\[ 4 \exp \left( \mu_{eff}(r_1 + r_2 + r) + (r_1 + 2r_2) \sqrt{\frac{c_{blood} \omega}{k}} \right) \times \]

\[ \pi r (u_0 - u_a) \left( -k \mu_{eff}^2 + c_{blood} \omega \right) \left( 1 + r_2 \sqrt{\frac{c_{blood} \omega}{k}} \right) \]

\[ 4 \exp \left( \mu_{eff}(r_1 + r_2 + r) + (2r_2 + r) \sqrt{\frac{c_{blood} \omega}{k}} \right) \times \]

\[ \pi r u_a \left( -k \mu_{eff}^2 + c_{blood} \omega \right) \left( 1 + r_2 \sqrt{\frac{c_{blood} \omega}{k}} \right) \]

\[/

\[ \{ 4 \pi r \left( -k \mu_{eff}^2 + c_{blood} \omega \right) \times \]

\[ \left( \exp \left( 2r_2 \sqrt{\frac{c_{blood} \omega}{k}} \right) \right) \left( 1 + r_2 \sqrt{\frac{c_{blood} \omega}{k}} \right) + \exp \left( 2r_1 \sqrt{\frac{c_{blood} \omega}{k}} \right) \left( 1 + r_2 \sqrt{\frac{c_{blood} \omega}{k}} \right) \} ] \]

\[ (5.4) \]
Table 5.1: Constitutive data [183, 226, 227]

<table>
<thead>
<tr>
<th>$k$ [$\text{W/mK}$]</th>
<th>$\rho$ [$\text{kg/m}^3$]</th>
<th>$c_{\text{blood}}$ [$\text{J/kgK}$]</th>
<th>$u_0$ [$^\circ\text{C}$]</th>
<th>$u_a$ [$^\circ\text{C}$]</th>
<th>$r_1$ [m$^{-1}$]</th>
<th>$r_2$ [m$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.527</td>
<td>1045</td>
<td>3840</td>
<td>21</td>
<td>37</td>
<td>7.5E-4</td>
<td>1</td>
</tr>
</tbody>
</table>

Discretization error of a point source array to approximate a line source

Here, a line source is approximated by an array of isotropic point sources evenly spaced along a 1.0 cm line segment. Increasing the number of isotropic point sources, $M$, provides a better approximation but increases the necessary computation time. One isotropic point source’s temperature profile is generated by the SSM kernel, Equation (5.4). Superposition is used to sum the temperature profiles of the isotropic point sources. First, the nominal power of the modeled ablation is evenly split by the number of isotropic point sources, $M$. The power of a single point source is then $P_{\text{single}}(M) = P/M$. The temperature field, $u(r)$, is given by summing the individual isotropic point sources, $u_i(r)$, while recalling that the temperature begins at $u_a$:

$$u(r) = u_a + \sum_{i=1}^{M} u_i(r), \quad u_i(r) = \frac{u_{h,i}(r)}{r} + \frac{u_{p,i}(r)}{r}. \tag{5.5}$$

In order to determine the number of isotropic point sources necessary to make an adequate approximation of a line source, an increasing number of isotropic point sources, $M = [1, 10, 15, 25, 50, 75, 100, 1E3, 1E4]$, was compared to a simulation assumed to be a perfect line source, $M = 1E5$. The simulation domain has two spatial dimensions and is further described in the next subsection.

Spatial domain of steady state model kernel

Any point in three dimensional space can have a temperature calculated by the SSM kernel, Equation (5.4). For a given set of bioheat and optical parameters, an isotropic point source’s temperature only depends on the Euclidean distance. Then, summing the $M$ temperature fields is trivial, as described in Equation (5.5). In this Chapter, the temperature prediction
is a two-spatial dimensional plane, i.e., single slice, discretized by pixels. That 2D field is compared with patient MRTI data. The simulation’s in-plane spatial domain matches a region of interest (ROI) selected from MRTI. In the simulation, the in-plane sampling is five times as dense as the MRTI’s. However, the MRTI’s single slice measurement comes from a finite thickness. Here, the SSM kernel models that finite thickness by averaging five simulation slices together. The middle simulation slice, slice 3, is registered to the MRTI slice location. The edge simulation slices, slices 1 and 5, are placed at the edges of the MRTI’s nominal slice thickness. Simulation slice 2 is exactly halfway between simulation slices 1 and 3, while simulation slice 4 is exactly halfway between simulation slices 3 and 5. In summary, the simulation’s spatial domain is oversampled five-fold in all three spatial dimensions, compared to whatever MRTI dataset is considered.

Using the described geometry, the SSM kernel calculates the distance, \( r \), between the \( M \) isotropic point sources and simulation’s sampled spatial points. That distance directly is substituted into Equation (5.4) and a temperature from each source point is known. Next, the simulation slices are averaged together. As part of the information recorded about the MRTI dataset’s ROI, the in-plane angle of rotation is available; the simulation’s in-plane ROI is rotated to match. The simulation ROI is designed to be large enough that after rotation, the simulation ROI can be cropped to match the MRTI’s ROI. Recall at this point, the simulation data is one slice, averaged together from five slices, and is oversampled by five-fold in both in-plane spatial dimensions, but the in-plane sampling points are rotated away from the MRTI’s pixel grid. The last geometric manipulation is to perform a two spatial dimensional interpolation — \texttt{interp2} in MATLAB — to re-grid the simulation ROI to match the MRTI’s pixel locations within the ROI. The ultimate result is the simulation’s spatial sampling points are in the exact spatial locations of the MRTI’s pixel centroids. The purpose of oversampling is to minimize spatial discretization error after rotation and re-gridding.
Temperature linearity with laser power

A convenient property of Equation (5.4) — and consequently Equation (5.5) — is that the temperature, \( u \), is linear with the laser's power, \( P \). Using a linear combination of simulations with zero power and a known power, a temperature field of arbitrary power can be generated: E.g., one 0 W temperature field and one 1 W temperature field can be linearly combined into a 15 W temperature field, or of any power desired. Ergo, the fact that patients receive different laser powers does not require the SSM to re-run with different powers, leading to tremendous speed advantages. Furthermore, the number of patients in the studied cohort does not change the number of SSM runs.

The equation to generate a temperature field of arbitrary laser power from 0 W and 1 W fields is

\[
u_2(\vec{x}) = u_1(\vec{x}) \cdot (P_2 - P_0) - u_0(\vec{x}) \cdot (P_2 - P_1) = (x_1, x_2) . \tag{5.6}
\]

Here, \( u_0(\vec{x}) \), \( u_1(\vec{x}) \), and \( u_2(\vec{x}) \) are respectively the in-plane temperature fields when \( P_0 = 0 \) W, \( P_1 = 1 \) W, and \( P_2 \) from the patient-specific laser power are used. \( \vec{x} \) is the two-dimensional, in-plane spatial location. Equation (5.6) is valid for any number of spatial dimensions. Another convenient implication of the power linearity is that the \( u_0(\vec{x}) \) temperature field can be reused for different values of \( \mu_{eff} \) as long as the bioheat parameters remain unchanged. Explicitly, if the bioheat parameters of Equation (5.1) — \( \omega \), \( \rho \), \( k \), \( c_{blood} \), \( c_p \), and \( u_a \) — remain the same, the same \( P = 0 \) W temperature field, \( u_0(\vec{x}) \), can be paired with any \( u_1(\vec{x}) \) in Equation (5.6) to produce \( u_2(\vec{x}) \). The reason this is possible is simple. \( \mu_{eff} \) can only affect the power term of Equation (5.4); when \( P = 0 \) W, \( \mu_{eff} \) does nothing.

5.2.4 Objective functions

The objective function is the Dice similarity coefficient (DSC) [9]. DSC is a metric that quantifies the overlap between two regions. In this application, the regions are thresholds of
damage. Damage can be indicated by Arrhenius damage, Section 2.3.1; cumulative equivalent minutes (CEM) damage, Section 2.3.3; or lethal threshold temperature damage model (LTTDM), Section 2.3.4. The LTTDM has relevance to this investigation and discussion can be found in Section 2.3.4; the chief reason is that the patient ablations are temporally short and reach high temperatures, i.e., $> 57^\circ C$. In this Chapter, however, Arrhenius dose with Henriques parameters is used in order to match Chapter 4. 

$$DSC = \frac{2|A \cap B|}{|A + B|}.$$ 

$A$ is the region circumscribed by the Arrhenius dose of $\Omega = 1$ from patient MRTI data. $B$ is the region enclosed by the $57^\circ C$ isotherm contour for the SSM kernel.

Alternate objective functions are available for consideration — namely, the $L_2$ norm of the MRTI compared to the model prediction and the Hausdorff distance — and are explored in Appendix C.

### 5.2.5 Global parameter search in $\mu_{eff}-\omega$ space

The simplifying approximations of the SSM kernel allow its computation to be very fast. The result is the SSM kernel can be optimized using a global parameter search, as opposed to methods that utilize one or more objective functions. The parameter search domain is a two-dimensional $\mu_{eff}-\omega$ space; blood perfusion and effective optical coefficient values are searched. The global parameter search scheme is a regular grid search within a densely sampled $\mu_{eff}-\omega$ space.

In the regular grid search, the perfusion space is $\omega \in [3, 16.5]$ $\text{kg m}^{-3} \text{s}^{-1}$ with 65 evenly spaced samples. The effective optical coefficient space is $\mu_{eff} \in [50, 400]$ $\text{m}^{-1}$ with 176 evenly spaced samples. The total number of $\mu_{eff}-\omega$ pairs is multiplicative; 65 $\omega$ samples $\times$ 176 $\mu_{eff}$ samples is 11,440 total $\mu_{eff}-\omega$ pairs. For the regular grid search, there are 11,440 $P = 1$ W simulations but only 65 $P = 0$ W simulations since varying $\mu_{eff}$ does
not change a $P = 0$ W simulation, as discussed beforehand.

### 5.2.6 Leave-one-out cross-validation and vector map manipulation

Similar to Chapter 4, leave-one-out cross-validation (LOOCV) is used here to simulate the $N + 1$ prediction case. However, the way that optimal $\mu_{eff} - \omega$ values are chosen during LOOCV is remarkably different. Described in Section 4.3.5, the previous method averages the parameter values that produced the optimal objective function performance in individual datasets; this creates a predictive parameter choice for the $N + 1$ dataset. Instead, access to the global behavior in $\mu_{eff} - \omega$ space provides far more powerful information.

Before LOOCV begins, the $\mu_{eff} - \omega$ global optimization using regular grid sampling is executed — described in Section 5.2.5. The result of optimization of a particular dataset is a 2D map in $\mu_{eff} - \omega$ space of the DSC performance. These maps of individual optimizations are superimposed to create a vector map of DSC performance among the datasets. It can also be conceived as a 3D dataset — one dimension of $\mu_{eff}$, one dimension of $\omega$, and one dimension of DSC performance among the datasets in cohort. The vector map is a mathematical entity critical to further analyses. Starting with the vector map, a variety of manipulations can be applied to interrogate the vector map. E.g., the mean, median, and standard deviation of the vector map respectively yield maps of the DSC’s mean, median, and standard deviation. A heuristic demonstration of the vector map’s construction is found in Figure 5.1. The vector map and its key position to understanding this Chapter can be explained as an analogy to the wave function in quantum mechanics. First of all, the wave function of quantum mechanics is the superposition of quantized, orthonormal states. Here, the vector map is the superposition of the DSC performance from the individual datasets. Second, once the wave function is known, an array of operators can be applied to find the expected values of a corresponding array of quantities of interest — e.g., position, momentum, and energy. Here, the vector map can be queried using descriptive statistics or DSC thresholds like the DSC $\geq 0.7$ limit demarking success/failure.
During one iteration of LOOCV of $N$ number of patients, a vector map is constructed using the $N - 1$ individual optimization maps. Then, a mean operator is applied to the 3D vector map, resulting in a 2D mean map. In this $N - 1$ DSC mean map, the $\mu_{\text{eff}} - \omega$ pairing that produces the greatest DSC is subsequently used to predict the left-out patient dataset; the predictive DSC performance is recorded. This concludes one iteration of LOOCV. The remainder of the LOOCV algorithm is to permute the left-out dataset until all datasets have been left out once.

In addition to tracking DSC performance in a vector map, the $L_2$ norm and the Hausdorff distance performance data are logged in their respective vector maps. Like the DSC vector map, the $L_2$ and Hausdorff distance vector maps can be queried using descriptive statistics, thresholds, or any other interesting manipulation. The results of these alternate objective functions, i.e., $L_2$ and Hausdorff distance, can be found in Appendix B.
Table 5.2: This table presents data regarding the convergence of the temperature field with increasing number of isotropic point sources, \( M \). The same data is found in Figure B.3. The leftmost column displays the number of isotropic point sources, \( M \). The remaining columns display the difference between a temperature field, \( u_{M} \), and a temperature field generated with \( M = 1E5 \) sources, \( u_{M=1E5} \). This difference is measured by the \( L_2 \) norm, and the maximum pixel-wise difference. The middle two columns are for temperature fields created using \( \mu_{\text{eff}} = 200 \text{ m}^{-1} \), while the right two columns use \( \mu_{\text{eff}} = 2000 \text{ m}^{-1} \). All simulations use \( \omega = 6.0 \text{ kg m}^{-3} \text{ s}^{-1} \) and parameter values from Table 5.1.

<table>
<thead>
<tr>
<th>( M )</th>
<th>( \mu_{\text{eff}} = 200 \text{ m}^{-1} )</th>
<th>( \mu_{\text{eff}} = 2000 \text{ m}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_2 ) norm</td>
<td>max ( {u_{M=1E5} - u_{M_2}}) (°C)</td>
<td>( L_2 ) norm</td>
</tr>
<tr>
<td>1</td>
<td>8.6139E3</td>
<td>6.6128</td>
</tr>
<tr>
<td>10</td>
<td>1.8825E2</td>
<td>-1.5909</td>
</tr>
<tr>
<td>15</td>
<td>78.359</td>
<td>-1.026</td>
</tr>
<tr>
<td>25</td>
<td>26.831</td>
<td>-0.60012</td>
</tr>
<tr>
<td>50</td>
<td>6.4661</td>
<td>-0.29444</td>
</tr>
<tr>
<td>75</td>
<td>2.8394</td>
<td>-0.19505</td>
</tr>
<tr>
<td>100</td>
<td>1.5871</td>
<td>-0.14580</td>
</tr>
<tr>
<td>1E3</td>
<td>1.5343E-2</td>
<td>-1.4334E-2</td>
</tr>
<tr>
<td>1E4</td>
<td>1.2660E-4</td>
<td>-1.3015E-3</td>
</tr>
<tr>
<td>1E5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 5.3: Here are the descriptive statistics for DSC performance during optimization — i.e., before cross-validation — for the $N = 22$ cohort. Steady state analysis using the $57^\circ C$ isotherm damage model is denoted SS. “opt.” refers to optimization during the regular grid search; “SS naive choice” refers to the performance using literature values with the SSM kernel. “FEM” refers to the optimization results from gradient-based optimization; the FEM results are the same as Chapter 4. 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 ascending ranked order.

<table>
<thead>
<tr>
<th>Descriptive Statistic</th>
<th>SS naive choice</th>
<th>FEM DSC opt.</th>
<th>SS DSC opt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.4986</td>
<td>0.4865</td>
<td>0.7224</td>
</tr>
<tr>
<td>25%-ile</td>
<td>0.6562</td>
<td>0.7394</td>
<td>0.8384</td>
</tr>
<tr>
<td>Median</td>
<td>0.7411</td>
<td>0.8142</td>
<td>0.8855</td>
</tr>
<tr>
<td>75%-ile</td>
<td>0.8183</td>
<td>0.8649</td>
<td>0.9156</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.8799</td>
<td>0.8972</td>
<td>0.9386</td>
</tr>
<tr>
<td>DSC ≥ 0.7</td>
<td>15</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>0.7197</td>
<td>0.7824</td>
<td>0.8666</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.1275</td>
<td>0.1091</td>
<td>0.06498</td>
</tr>
<tr>
<td>Skewness</td>
<td>-1.020</td>
<td>-1.332</td>
<td>-1.014</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>3.349</td>
<td>4.005</td>
<td>2.895</td>
</tr>
</tbody>
</table>
Table 5.4: Here are the descriptive statistics for DSC performance during LOOCV for the $N = 22$ cohort. Steady state analysis using the 57°C isotherm damage model is denoted SS. “LOOCV” refers to the prediction results during the cross-validation of the trained SSM and FEM methods; “SS na"ïve choice” refers to the performance using literature values with the SS kernel. “FEM” refers to the LOOCV results after gradient-based optimization; the FEM results are the same as Chapter 4. This Table’s data is also presented in Figure 5.4. 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 ascending ranked order.

<table>
<thead>
<tr>
<th>Descriptive Statistic</th>
<th>SS na&quot;ïve choice</th>
<th>FEM DSC LOOCV</th>
<th>SS DSC LOOCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.2988</td>
<td>0</td>
<td>0.4791</td>
</tr>
<tr>
<td>25%-ile</td>
<td>0.5965</td>
<td>0.6709</td>
<td>0.7143</td>
</tr>
<tr>
<td>Median</td>
<td>0.6564</td>
<td>0.8001</td>
<td>0.8297</td>
</tr>
<tr>
<td>75%-ile</td>
<td>0.7595</td>
<td>0.8429</td>
<td>0.8787</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.8575</td>
<td>0.8859</td>
<td>0.9186</td>
</tr>
<tr>
<td>DSC $\geq$ 0.7</td>
<td>9</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td>0.6513</td>
<td>0.7323</td>
<td>0.7771</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.1429</td>
<td>0.1930</td>
<td>0.1288</td>
</tr>
<tr>
<td>Skewness</td>
<td>-0.84288</td>
<td>-2.830</td>
<td>-0.9241</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>3.241</td>
<td>9.919</td>
<td>2.961</td>
</tr>
</tbody>
</table>
Figure 5.1: This is a cartoon demonstration of the superposition of individual datasets’ global optimizations in $\mu_{\text{eff}} - \omega$ space. Each dataset’s optimization performance, e.g. (A) and (B), can be superimposed pixel-wise in $\mu_{\text{eff}} - \omega$ space to create an optimization vector map (C). This optimization vector map has $N = 22$ individual optimization results for every point in $\mu_{\text{eff}} - \omega$ space. At every point in the optimization vector map, descriptive statistics can describe the distribution’s behavior at that $\mu_{\text{eff}} - \omega$ point, see Figure 5.2. This is roughly analogous to the superposition of wave functions to describe the state of an atom using quantum mechanics and then using operators to find interesting quantities.
5.3 Results

5.3.1 Characterization of steady state model kernel

The temperature from a single isotropic point source is plotted in Figure B.1. There is a temperature buildup from the \( r_1 \) boundary up to the peak followed by a temperature decay out to the \( r_2 \) boundary. The behavior of the steady model while the number of source points, \( M \), increases is shown in Figures B.2 and B.3 and Table 5.2. Table 5.2 demonstrates that maximum pixel-wise difference reduces linearly with increasing \( M \). The \( \mu_{eff} = 200 \text{m}^{-1} \) portion of Table 5.2 is the more relevant data; however \( \mu_{eff} = 2000 \text{m}^{-1} \) provides a worst case scenario. \( M = 50 \) has an acceptable balance of simulation fidelity and computation time and is used in the subsequent simulations. The maximum pixel-wise difference between \( M = 50 \) and \( M = 1E5 \) is 0.29444 \( ^\circ \text{C} \). Figure B.4 is a demonstration of the SSM kernel’s linearity with power. A difference image between a 15 W image directly generated by the kernel and a 15 W image generated by 1 W and 0 W images shows that the methods are equivalent.

5.3.2 Optimization

The optimization performance is best summarized in the “SS DSC opt.” column of Table 5.3. The mean DSC performance was 0.8666 with all 22 patient datasets passing DSC \( \geq 0.7 \) during optimization. Individual optimization maps can be found throughout Appendix A. Optimization of the alternate objective functions, i.e., the \( L_2 \) and Hausdorff distance, are found in Figures B.5 and B.6 of Appendix B. The optimal mean Hausdorff distance is 4.732 mm. By comparing Figures 5.2A and B.6, the regions of superior performance in both Figures overlap in \( \mu_{eff} - \omega \) space — i.e., the areas of smallest mean Hausdorff distance overlaps with the areas largest mean DSC. The \( L_2 \) map of Figure B.5 has a similar shape; however, the optimal \( L_2 \) region is shifted right (increasing \( \mu_{eff} \)) relative the optimal regions of the optimal DSC and Hausdorff distance regions.
5.3.3 Leave-one-out cross-validation performance

Using the vector map method for parameter selection described in Section 5.2.6, the LOOCV performance is detailed in Table 5.4. The SSM kernel performs definitively better after training — DSC mean = 0.7771 and 17 of 22 pass DSC ≥ 0.7 — as opposed to using naïve literature values — DSC mean = 0.6513 and 9 of 22 pass DSC ≥ 0.7. Meanwhile, the trained FEM model of Chapter 4 has a mean DSC of 0.7323 and passes 15 of 22.

<table>
<thead>
<tr>
<th>Mean (A)</th>
<th>Median (B)</th>
<th>Standard deviation (C)</th>
<th>Passing (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Mean Map" /></td>
<td><img src="image2" alt="Median Map" /></td>
<td><img src="image3" alt="Std Dev Map" /></td>
<td><img src="image4" alt="Pass Map" /></td>
</tr>
</tbody>
</table>

Figure 5.2: These are the descriptive statistic maps based on the vector map, described in Figure 5.1. The ‘x’ marks the naïve literature value choice, $\mu_{eff} = 180 \text{ m}^{-1}$ and $\omega = 6 \text{ kg m}^{-3} \text{s}^{-1}$. (A) is the mean; (B) is the median; (C) is the standard deviation; (D) is the pass rate — i.e., DSC ≥ 0.7.
5.4 Discussion

The accuracy achieved by the steady state model (SSM) is driven by two interrelated factors. First, the GPU-accelerated SSM kernel’s prodigious speed empowers a better approximation of the line source by using $M = 50$ point sources and the exhaustive, dense sampling of the $\mu_{\text{eff}}-\omega$ parameter space. Secondly, the 2D global optimization enables a far more effective LOOCV algorithm, i.e., the vector map optimization. The difference in Chapter 4’s LOOCV algorithm and this Chapter can be understood as the difference between optimizing the datasets individually versus optimizing all datasets mutually and simultaneously. The mutual optimization during LOOCV via the vector map results in $\mu_{\text{eff}}-\omega$ parameter choices that favor overall performance as opposed to expecting the average of individual optimizations to produce quality performance among all datasets. The most striking result of Chapter 5 is that more exhaustive training can empower a relatively simple model to perform similar to a more sophisticated model with less exhaustive training — i.e., Appendix C’s comparison of the SSM kernel with exhaustive sampling of $\mu_{\text{eff}}-\omega$ space versus the FEM kernel with gradient-based optimization of $\mu_{\text{eff}}$ space.

A remarkable advantage of the presented GPU-accelerated, vector map LOOCV method is that it heavily employs lookup tables and saved data. The 1 W and 0 W images are generated by the SSM kernel and saved; the kernel is then no longer used. By taking advantage of the model’s linearity with laser power, the 1 W and 0 W images can match an arbitrary single slice MRTI dataset by adjusting the power and in-plane laser fiber angle of orientation. The technique saves time by avoiding the need to run the kernel for each individual dataset; instead, it runs through every $\mu_{\text{eff}}-\omega$ pairing once for all datasets. The other time-saving feature is the LOOCV algorithm is provided by lookup tables. For every $\mu_{\text{eff}}-\omega$ pairing, the various objective functions are recorded. The data array represented by an exhaustive list of $\mu_{\text{eff}}-\omega$ pairings and the subsequent objective functions among the
$N$ number of patient datasets is the vector map; the size of the vector map is

$$V_{size} = N_{\mu eff} \times N_\omega \times N$$

where $V_{size}$ is the total number of elements in the vector map, $N_{\mu eff}$ is the number of $\mu eff$ samples, $N_\omega$ is the number of $\omega$ samples, and $N$ is the number of patients in the cohort. Executing the LOOCV algorithm is then trivial. For one LOOCV iteration, simply drop one patient dataset from the vector map, create a mean map by averaging, and find the maximum DSC value of the $N - 1$ mean map. The entire LOOCV algorithm is then only manipulations of a lookup table, i.e., the vector map.

Besides the use of the time-saving vector map LOOCV method, the train-and-predict algorithm’s use is simplified by the order of computational tasks. The generation of 1 W and 0 W images for each $\mu eff$–$\omega$ point by the SSM kernel is the longest single computation, taking 2.14E4 s and occurs first. The GPU is only used for the SSM kernel calculations. The subsequent operations to register the 1 W and 0 W images and record the objective functions is executed on CPU and takes 1.28E3 s per patient dataset — 3.85E4 s for the 30 datasets described in Appendix A. This means that adding more datasets to the cohort only takes about 1.28E3 s (∼21 min) for new entries.

The advantage of global optimization of individual datasets superimposed into a vector map is exemplified by comparing to an alternative gradient-based optimization of the mean DSC among $N - 1$ datasets. In this alternative case, a $\mu eff$–$\omega$ value is submitted to the kernel for $N - 1$ number of times; the mean DSC is recorded. The gradient-based optimization then requests more $\mu eff$–$\omega$ values to run among the $N - 1$ individuals in an effort to maximize DSC. Once the gradient-based algorithm converges and reports a maximum DSC, the corresponding $\mu eff$–$\omega$ value is used on the $N^{th}$ dataset for the predictive case and the DSC is recorded. That procedure must be repeated $N$ number of times. A back-of-the-envelope estimation of the number of realizations a gradient-based
algorithm must do to maximize DSC among all datasets is an inaccurate but illustrative exercise. If there are $N = 22$ datasets, then the gradient-based optimization must interrogate $N - 1 = 21$ datasets to execute a single iteration of the gradient-based optimization. Supposing the gradient-based optimization requires only 10 iterations (very favorable to the gradient-based optimization) to find the maximum DSC for the $N - 1$ datasets, then the total number of SSM kernel realizations is

$$N_{grad\,opt} = N \times (N - 1) \times M_{iter} = 22 \times 21 \times 10 = 4,620$$

where $N_{grad\,opt}$ is the total number of kernel realizations (4,620) necessary to execute LOOCV while optimizing the mean DSC among $N - 1$ datasets. $N$ is the number of patient datasets (22) and $M_{iter}$ is the assumed number of iterations for the gradient-based optimization to converge (10). While the gradient-based LOOCV requires about a third the quantity of realizations as the global optimization–vector map method, the gradient-based LOOCV algorithm is considerably less flexible than the vector map LOOCV. Consider the case where the patient cohort is modified. If patients are added or subtracted or swapped into the $N = 22$ cohort, the optimization space is modified and the gradient-based method must begin anew. In contrast, the vector map LOOCV algorithm just changes the vector map, which is a simple matrix manipulation. To be fair to the gradient-based method when faced with modified patient cohorts, there exist shortcuts to expedite the optimization, but the gestalt is that gradient-based optimization is an unwieldy method to maximize the mean DSC for LOOCV. Finally, the gradient-based method is discussed because it was used in Chapter 4’s FEM model implementation; however, other objective functions that minimize an objective function, such as a pattern search algorithm, face the same challenges.

Fundamentally, the success or failure of the trained SSM kernel is driven by the individual datasets’ DSC performance in response to different $\mu_{eff} - \omega$ values. Broadly speaking, a cohort which leads to successful prediction during LOOCV requires that the successful
parameter values are similar amongst the individual datasets in the cohort. Appendix A exhibits that quality as the lion’s share of datasets’ DSC ≥ 0.7 regions have overlapping $\mu_{eff} - \omega$ values. Perhaps then, it may be argued that the failing datasets should be excluded. However, there is no a priori method available in this investigation of identifying that certain datasets does not belong with the others. In fact, all 22 datasets have optimal DSC values ≥ 0.7.

Within this investigation, more metrics beyond DSC are available and the data is shown within Appendix B. The $L_2$ metric’s best region in $\mu_{eff} - \omega$ space does not overlap with the other metrics’ optimal regions. This is believed to occur because the $L_2$ metric is a spatially global measure — i.e., every pixel in the ROI is included — whereas the Hausdorff distance and DSC metrics are thresholded by the 57 $^\circ$C isotherm. Hence, it is possible for a superior DSC value to manifest while the $L_2$ metric performs relatively poorly because the region inside the 57 $^\circ$C isotherm is too hot and the region outside the 57 $^\circ$C isotherm be too cold. The chief interest here is matching the damaged regions, and consequently the $L_2$ norm is not found to have as much value. Nonetheless, the $L_2$ norm’s global optimization shape in $\mu_{eff} - \omega$ space is found to corroborate the shape of the global performance of the DSC and Hausdorff metrics via the comparison of Figures 5.2A, B.5, and B.6. Regarding the information yielded by the Hausdorff metric, the Hausdorff metric is the spatial distance-to-agreement between the 57 $^\circ$C isotherms from the model and patient MRTI data. By using a combination of DSC and Hausdorff distance, two commonsense questions about the goodness-of-fit between the model prediction and MRTI are addressed. The DSC indicates the fraction of overlap while the Hausdorff distance indicates the distance-to-agreement for the most distant discrepant pixel. By that standard, the mean LOOCV performance is > 0.75 DSC and < 5.0 mm Hausdorff distance. The median Hausdorff distance is considerably smaller at < 3.9 mm because the median is not sensitive to outliers, the most egregious being #0495.

The Hausdorff distance allows a comparison to a gold-standard intervention for brain
metastases: stereotactic radiosurgery (SRS). A common goodness-of-fit metric in radiation therapy is the gamma metric; it has two sub-metrics that compare a planned radiation dose field to a measured field. According to the gamma metric, SRS is considerably more precise as definitive treatment of brain metastases via Gamma Knife is characterized by a distance-to-agreement well under 1 mm [246]. However, the two interventions are not meant to be compared head-to-head for the same treatment task. SRS for brain metastases is the first-line treatment whereas MRgLITT is palliative. It is worth recalling, however, that patients treated with MRgLITT are unlikely to succumb due to brain metastases as long as they are able and willing to undergo more surgery.

Reaching a LOOCV prediction accuracy of 17 of 22 passing DSC ≥ 0.7 through a computational technique that can be easily executed within two days represents progress in the effort to create clinically useful MRgLITT predictions. In order to improve further, there are a variety of deficiencies and corresponding investigations that can be done. First of all, the registration lacked out-of-plane spatial information. Naturally, MR images that provide 3D morphological data of the laser fiber and the target would be useful. Secondly, more patient datasets would provide more reliable results. Thirdly, it might be critical to know more about the disease state. As it stands, it was only known that patients were afflicted with brain metastases. Knowledge of the metastasis’ origin, e.g. lung vs. breast vs. melanoma, or its location, e.g., temporal cerebrum vs. midbrain, may allow the datasets to be grouped into subcohorts with superior predictive power. These three modifications are relatively straightforward to implement if the necessary data were available; i.e., there are no significant changes to the SSM kernel or the LOOCV execution.

While the previous three modifications are likely beneficial and manageable, more radical improvements are necessary to adequately predict dramatically heterogeneous/asymmetric ablations. Describing the SSM kernel disparagingly, the kernel is an ellipsoid with a size determined by laser power, effective optical coefficient, and microperfusion rate. A review of Appendix A shows that the simple kernel can succeed for a variety of situations,
ultimately the kernel simply cannot conform to ablation shapes that appreciably deviate from an ellipsoid; it simply cannot recapitulate the variety of observed clinical ablations in brain. To move laser ablation modeling forward to translation, a kernel must be able to recapitulate asymmetric shapes. One solution is to use kernels that are considerably more sophisticated than the SSM kernel. An excellent example would include finite element method models that use damage-dependent tissue parameters and convective boundary conditions like [62]. However, such complex models are profoundly more difficult to train which undermines the maximum achievable prediction accuracy. The SSM kernel may still be effective in the presence of convective boundaries if two primary challenges are met. First, the kernel must be able to modified to conform to convective boundaries; perhaps boundary conditions can be added to the GPU-accelerated kernel. Second, the training from prior datasets that have different boundary conditions must remain effective in kernel implementations of yet more novel differing boundary conditions.

5.5 Conclusion

It has been demonstrated that a relatively simple kernel can perform relatively well if it is given the opportunity for effective parameter training. The dramatic enhancement of accuracy motivates the implementation of model training as available in the future.

Declaration of interest

This research was supported in part through a grant from the National Center for Advancing Translational Sciences of the National Institutes of Health, TL1TR000369.
Figure 5.3: This is a scatter plot indicating the locations of the optimal $\mu_{eff} - \omega$ pair for each dataset among the $N = 22$ datasets. There is a least-squares line fit (in blue) of the 21 optimal points (markers are blue with green outlines) that define the line. There is one clearly outlying optimal point are marked in green exclusively. It is from 495 and can be viewed in Figure A.1. The scatter plot and fit line are superimposed over the mean of vector map, i.e., Figure 5.2(A).
Figure 5.4: The predictive performance — as measured by DSC — is compared for the three models. In blue, is the steady state model using naïve literature values. In red, is the FEM model’s performance. Last and in green, is the globally optimized, trained state model.
Chapter 6

Conclusion

Magnetic resonance-guided laser induced thermal therapy (MRgLITT) is finding favor with neurosurgeons as a minimally invasive intervention in management of cancer and epilepsy. The surgical placement of the laser fiber stands to benefit from a computer modeling system that can indicate the largest probable laser ablation a priori. Chapter 2 described the history, significance, and key concepts of thermal therapy and laser-induced thermal therapy in particular. Chapters 3, 4, and 5 are steps in the process of creating a predictive model despite the dearth of available parameter data: identification of sensitive model parameters, model calibration, and model validation. Within the $N = 22$ cohort examined in Chapters 4 and 5, the calibrated SSM did not meet the Hypothesis’ success criteria; however, the trained model was shown to effectively improve the predictive performance. Within the better-vetted $N = 20$ cohort examined in Appendix C, the trained steady state model (SSM) succeeds at the standard set by the Hypothesis. Critically, the $N = 20$ cohort aims to only include datasets that are steady state or nearly steady state, matching the assumptions of the SSM.

Nonetheless, at least two difficult tasks must be overcome before a model would be remotely considered as ready for a priori planning. First, the datasets within both cohorts had only one image plane available to analyze; a multi-slice dataset with three spatial dimensions would be preferred to ensure that the modeling is sufficiently accurate beyond
one image plane. Second, none of the datasets within either cohort exhibited convective heat loss associated with a relatively large blood vessel or brain ventricle, a major challenge in MRgLITT planning. A successful model should handle these convective boundaries, or at least the boundaries should be identified \textit{a priori} with a high degree of confidence.

Chapter 3’s motivating concept is that quantifying the input parameter uncertainty and propagating that uncertainty to the temperature field would engender stochastic predictions that did not require perfect accuracy. Such a probabilistic prediction is useful if the accurate prediction occurs with reasonably high probability and a large majority confidence interval — e.g., 95\% or 99\% CI — remains within an acceptable tolerance. The results of Chapter 3 report probabilistic temperature fields with measures of central tendency, i.e., mean and median, that are near the desired marks based on MR temperature imaging in normal canine brain and canine prostate fixed in agar gel. The 95\% CI of the probabilistic temperature predictions manifest variances that are too large to consider Chapter 3’s stochastic model as sufficiently precise for clinical predictions. The stochastic temperature predictions are essentially too imprecise given the available literature values. However, regarding the first Specific Aim, the results demonstrate that the most sensitive model parameters are within the three optical parameters. The variance of thermal conductivity and blood microperfusion are similar in magnitude, but microperfusion’s variance is greater beyond $\sim 2 \text{ mm}$.

The lack of precision in Chapter 3’s results immediately motivate the train-and-predict paradigms in Chapters 4 and 5 and indicate what model parameters should be optimized. The purpose of calibration — i.e., parameter optimization or model training — is to provide parameter data to the model during subsequent prediction. Training circumnavigates the need to ascertain higher quality physical measurements of constitutive values, i.e., thermal conductivity, microperfusion rate, and optical coefficients. Furthermore, training somewhat avoids the task of defining what a quality measurement must be; e.g., “Does the measurement need to be \textit{in vivo}, disease-specific, or even patient-specific?” Instead,
new questions emerge regarding the number of training datasets necessary for accurate prediction and defining subcohorts of parameters. Nonetheless, optimizing a model with MRTI data from a variety of patients seems a much more tractable challenge than acquiring physical measurements of constitutive values from a sufficiently large and diverse group of patients.

The other chief feature of Chapters 4 and 5 is the use of LOOCV to simulate the prediction of the $N+1$ patient, which provides an avenue to compare the many conceivable models of varying complexity. Now then, there emerge two train-and-predict paradigms; each may be used with or without uncertainty quantification provided via gPC.

1. **Optimize individual datasets; then use LOOCV**
   
The gradient-based optimization method from Chapter 4 and discussed in Appendix C is an example of optimizing individual datasets, average the individual optimal parameter values, and then emulate prediction of the $N+1$ dataset by using LOOCV. The advantage of this paradigm is that as the patient cohort changes, datasets that have already been optimized do not have to be reexamined. This paradigm is amenable to a gradient-based optimization. The disadvantage is this paradigm relies on the assumption that the average of the individual optimal model parameters is a surrogate for the optimization of the mean objective function among the cohort.

2. **Mutually optimize cohort; then use LOOCV**
   
This is the paradigm that motivates the vector map. The optimization is with respect to the mean of objective function among all datasets. Since mutual optimization of the cohort is a more complex task than optimizing individual datasets, this paradigm is better suited for relatively simple kernels. As discussed previously, optimization schemes besides the vector map can be used. The vector map represents a very convenient method of execution.

If gPC is chosen to be integrated into these train-and-predict paradigms, the distri-
bution of trained parameters can be used to create an empirical probability distribution function (PDF) that in turn can be fitted to a PDF from the Wiener–Askey scheme via some means, e.g., moment matching. The treatment of stochastic predictions may require further consideration to understand the best use of such spatio-temporally plural information. A common-sense approach would be to look at the behavior of the measures of central tendency, with preference to the median — i.e., the most typical realization. Secondly, examining the worst case scenario or a surrogate of the worst case scenario that has an appreciable probability to realize — e.g., the 10%, 5%, or 1% worst case realizations. The application of stochastic predictions can empower predictions during cross validation or during a truly naïve $N + 1$ predictive scenario. If a hypothetical trained kernel were able be successful in cross validation where success was defined by passing the 5% worst case realization, such a kernel could go into a clinical observational study or randomized controlled trial with a high confidence of success. Any optimistic speculation regarding the incorporation of gPC within the prediction hinges on how similar or different the empirical PDF conforms to a Wiener–Askey scheme distribution.

Another exciting future direction is the incorporation of more imaging data into the model training process. First of all, three dimensional spatial data can inform and improve the laser fiber registration, as discussed earlier. A second opportunity for the use of MRI images is to non-invasively measure the magnitude of microperfusion. Either arterial spin labeling (ASL) or dynamic susceptibility imaging-MRI (DSC-MRI) can acquire such information, each MRI perfusion modality with its own challenges [247,248]. A third, and arguably the most critical, addition of information from MRI is the inclusion of tissue labels into the model training procedure. Using either tissue segmentation from neuroradiologists or an algorithmic segmentation [245], the model training can expand from a homogeneous, one-label optimization to a heterogeneous, multi-label optimization.

If it is postulated that laser modeling is predictive within a clinically tolerable margin, a final mitigating consideration is the uncertainty that faces all proposed interventions.
Even if a hypothetical trained kernel is predictive in the clinic, what good does it do? Does accurate modeling/planning provide an effectual benefit to patients in randomized controlled trials? If the kernel is predictive, does it improve survival? Progression-free survival? Surgical complication rate? Time length of surgical intervention? Quality-of-life? Cost? An increase in stimulation of the neurosurgeon’s zygomaticus major muscle? Careful prospective clinical trial design is necessary to isolate the effect of a predictive model applied to surgical planning in MRgLITT. Nevertheless, if progress is to be forged, research efforts must be made while the outcome is most uncertain.
Appendix A: 2D optimization of MRTI datasets

This Appendix shows four subfigures for each of the 30 MRTI datasets available. Further discussion can be found in Section 5.2.2 and Tables C.1 and C.2. Subfigure (A) is the model’s temperature prediction; Subfigure (B) is the MRTI at the hottest time point; Subfigure (C) is the damage indicated by the lethal threshold temperature damage model (LTTDM) using 57°C as the threshold; Subfigure (D) is the result of the regular grid search described in Section 5.2.5. Subfigure (D) also includes a blue dot with a green outline that indicates the point in $\mu_{eff}\omega$ space that has the optimal DSC value. The MRTI datasets are listed in the following order: first, the most puzzling dataset, #0495; second, the two datasets that are included in the $N = 22$ cohort but excluded in the $N = 20$ cohort; third, the eight datasets that are excluded in both cohorts; fourth, the twenty datasets that are included in both cohorts.
Figure A.1: MRTI #0495 FOV: 37.480 mm × 42.165 mm. Maximum DSC in optimization: 0.90359. This MRTI dataset is the only one that was failed to be predicted with a DSC ≥ 0.7. It is included in both 20 and 22 dataset lists. A failure prediction simply means that the average of \( \mu_{\text{eff}} \) and \( \rho \) from the training was not similar to this dataset’s optimal \( \mu_{\text{eff}} \) and \( \rho \). That result can be seen by reviewing subfigure (D); the passing regions are far from all the other datasets’ passing regions. Why there is this separation of passing regions is puzzling. Dataset #0495 appears to be in-plane; the MRTI time series suggest that the ablation is near steady state. In short, #0495 appears to be the perfect ablation archetype.
Appendix A: Datasets included in the $N = 22$ cohort but excluded from the $N = 20$ cohort

(A) (B) (C) (D)

Figure A.2: MRTI #0415 FOV: 16.866 mm $\times$ 14.992 mm. Maximum DSC in optimization: 0.86111.
Figure A.3: MRTI #0435 FOV: 25.770 mm × 25.770 mm. Maximum DSC in optimization: 0.76018.
Figure A.4: MRTI #0440 FOV: 29.206 mm × 27.488 mm. Maximum DSC in optimization: 0.71809.
Figure A.5: MRTI #0447 FOV: 28.110 mm × 29.047 mm. Maximum DSC in optimization: 0.76636.
Appendix A: Datasets excluded from the $N = 22$ cohort but included in the $N = 20$ cohort

Figure A.6: MRTI #0436 FOV: 34.360 mm $\times$ 25.770 mm. Maximum DSC in optimization: 0.85827.
Figure A.7: MRTI #0457 FOV: 28.110 mm × 28.110 mm. Maximum DSC in optimization: 0.87368.
Appendix A: Datasets excluded from both cohorts

Figure A.8: MRTI #0497 FOV: 18.740 mm × 18.740 mm. Maximum DSC in optimization: 0.80000. This ablation clearly did not reach steady state.
Figure A.9: MRTI #0409 FOV: 28.110 mm × 28.110 mm. Maximum DSC in optimization: 0.080000. This ablation clearly was a test pulse.
Figure A.10: MRTI #0466 FOV: 17.180 mm × 15.462 mm. Maximum DSC in optimization: 0.70370.
Figure A.11: MRTI #0468 FOV: 20.616 mm × 20.616 mm. Maximum DSC in optimization: 0.50000.
Figure A.12: MRTI #0471 FOV: 17.180 mm × 18.898 mm. Maximum DSC in optimization: 0.60274.
Figure A.13: MRTI #0476 FOV: 25.770 mm × 25.770 mm. Maximum DSC in optimization: 0.77095.
Appendix A: Included datasets in both cohorts

(A)  

(B)  

(C)  

(D)  

Figure A.14: MRTI #0417 FOV: 25.77 mm × 27.488 mm. Maximum optimal DSC: 0.74713.
Figure A.15: MRTI #0477 FOV: 34.360 mm × 34.360 mm. Maximum DSC in optimization: 0.90104.
Figure A.16: MRTI #0488 FOV: 37.480 mm × 32.795 mm. Maximum DSC in optimization: 0.87982.
Figure A.17: MRTI #0491 FOV: 24.362 mm × 23.425 mm. Maximum DSC in optimization: 0.84839.
Figure A.18: MRTI #0496 FOV: 24.362 mm × 24.362 mm. Maximum DSC in optimization: 0.93889.
Figure A.19: MRTI #0490 FOV: 19.756 mm × 18.858 mm. Maximum DSC in optimization: 0.89842.
Figure A.20: MRTI #0378 FOV: 9.3700 mm × 14.055 mm. Maximum DSC in optimization: 0.82443.
Figure A.21: MRTI #0402 FOV: 37.480 mm × 42.165 mm. Maximum DSC in optimization: 0.91258.
Figure A.22: MRTI #0389 FOV: $32.795 \text{ mm} \times 32.795 \text{ mm}$. Maximum DSC in optimization: 0.91257.
Figure A.23: MRTI #0385 FOV: 28.110 mm × 28.110 mm. Maximum DSC in optimization: 0.92704.
Figure A.24: MRTI #0438 FOV: 25.770 mm × 20.616 mm. Maximum DSC in optimization: 0.86430.
Figure A.25: MRTI #0455 FOV: 28.110 mm × 28.110 mm. Maximum DSC in optimization: 0.89150.
Figure A.26: MRTI #0453 FOV: 39.354 mm × 39.354 mm. Maximum DSC in optimization: 0.94763.
Figure A.27: MRTI #0450 FOV: 37.480 mm × 37.480 mm. Maximum DSC in optimization: 0.90377.
Figure A.28: MRTI #0451 FOV: 20.614 mm × 20.614 mm. Maximum DSC in optimization: 0.95307.
Figure A.29: MRTI #0418 FOV: 34.360 mm × 25.770 mm. Maximum DSC in optimization: 0.91066.
Figure A.30: MRTI #0414 FOV: 16.866 mm × 21.551 mm. Maximum DSC in optimization: 0.88095.
Appendix B: Additional results for Chapter 5

This Appendix shows additional results from Chapter 5 regarding the convergence of the steady state model (SSM) kernel with increasing $M$ source points, the power linearity of the SSM kernel, and the secondary objective functions ($L_2$ and Hausdorff distance).

The primary objective function for the SSM with global optimization is the DSC between the SSM’s predicted 57°C isotherm and the MRTI’s Arrhenius dose $\geq 1$ using Henriques and Moritz’ dose model parameters. The secondary objective function is similar to the first: the DSC between the SSM’s predicted 57°C isotherm and the MRTI’s 57°C isotherm. The primary and secondary objective functions are shown in Appendix A on an individual optimization basis, as opposed to a global optimization.

Besides the two previous and highly related objective functions, there are two more objective functions available for consideration. The first is the $L_2$ norm between the two temperature fields — i.e., the MRTI compared to the SSM prediction. The second is the Hausdorff distance [249]:

$$d_H(A, B) = \max \left\{ \sup_{a \in A} \inf_{b \in B} d(a, b), \sup_{b \in B} \inf_{a \in A} d(a, b) \right\}.$$  

$d_H(A, B)$ is the Hausdorff distance between regions $A$ and $B$; $A$ and $B$ have the same definitions as in the DSC definition. “inf” is the infimum and “sup” is the supremum of set theory. $a$ is a pixel from the set $A$, and $b$ is a pixel from the set $B$. $d(a, b)$ is then the Euclidean distance between a pixel from set $A$, and a pixel from set $B$. 
Figure B.1: This is a one-dimensional temperature field from a single isotropic point source, as calculated with Equation (5.4). The constitutive values are from Table 5.1 with $\mu_{eff} = 200 \text{ m}^{-1}$, $\omega = 6.0 \text{ kg m}^{-3} \text{ s}^{-1}$, and $P = 12 \text{ W}$. The red hash mark is the $r_1 = 0.00075 \text{ m}$ boundary for the cooling fiber where $u(r_1) = u_0 = 21 ^\circ \text{C}$. As $r$ increases, the temperature, $u(r)$, builds up to the peak and falls back to $u(r_2) = u_a = 37 ^\circ \text{C}$. In the case of $M$ number of isotropic point sources, the power is divided among the $M$ points evenly as discussed earlier.
Figure B.2: These figures demonstrate of increasing $M$ sources to approximate a line source. The top row are the temperature fields from simulations using $M = 1$, $M = 10$, and $M = 1E5$ sources; $M = 1E5$ sources is assumed to perfectly approximate a line source. The bottom row shows the difference in temperature fields generated by $M = 1E5$ and $M = 1$, $M = 10$, and $M = 1E4$ sources. Notice that with as little as $M = 10$ sources, the shape of the temperature maps appear to emulate the $M = 1E5$ temperature map. However, the second row shows pixel-wise differences varying from $\sim -0.5 ^\circ C$ to $\sim +3 ^\circ C$ for $M = 10$, whereas the $M = 1E4$ case variance is about $1/1000th$ versus $M = 10$. 
Figure B.3: The two plots demonstrate the convergence from increasing the number of isotropic source points by comparing $M = 1\times10^5$ and $M = [1, 10, 15, 25, 50, 75, 100, 1\times10^3, 1\times10^4]$. All simulations use $\omega = 6.0\text{ kg m}^{-3}\text{s}^{-1}$ and Table 5.1 values. (A) uses $\mu_{eff} = 200\text{ m}^{-1}$ while (B) uses $\mu_{eff} = 2000\text{ m}^{-1}$. The horizontal axis is the number of source points, $M$. The left vertical axis is the log$_{10}(L_2)$, a metric sensitive to the entire temperature fields being compared. The right vertical axis is the max {$\log_{10}(\vert u_{M=1\times10^5} - u_{M=1\times10^4} \vert)$}, which is a surrogate of the maximum pixel-wise difference.
Figure B.4: The figures demonstrate the property of power linearity for the SSM kernel using Equation (5.6). The top row shows 2D temperature fields from 0 W and 1 W power settings. The bottom figure is the linear combination of the top two figures to generate a 15 W temperature field. Compared to a temperature field generated by directly using $P = 15$ W, the $L_2$ norm is $1.2578E-3$ and the maximum pixel-wise difference is $1.8495E-5$ °C. For the temperature scale of all three subfigures, 0 °C on the scale is set to body temperature, or 37 °C.
Figure B.5: For the $N = 22$ cohort, this Figure displays the mean map of the 2D regular grid optimization with respect to $L_2$. The general shape of the optimal region — i.e., the minimal region of $L_2$ — is very similar to the DSC mean and median maps of Figures 5.2(A) and (B). However, the optimal regions of this $L_2$ is not coincident with the optimal DSC regions.
Figure B.6: For the $N = 22$ cohort, this Figure displays the mean map of the 2D regular grid optimization with respect to Hausdorff distance. The general shape of the optimal region — i.e., the minimal region of Hausdorff distance — is very similar to the DSC mean and median maps of Figures 5.2(A) and (B). Here, the optimal region of Hausdorff distance is coincident with the optimal DSC regions.
Appendix C: Alternate patient cohort and validation results

This Appendix is a method redux of Chapter 5’s steady state model (SSM). Namely, the unique contribution is to create a cohort that is best suited to the SSM. The primary distinction between this Appendix’s cohort and the $N = 22$ cohort used in Chapters 4 and 5 is that the included datasets reach, or very nearly reach, steady state.

Within the entire dissertation, there are two analyzed cohorts of patient datasets. Both groups are selected from an available list of 30 datasets. Of those 30, eight were excluded for the work in Chapters 4 and 5 [67]; a cohort of $N = 22$. Since Fahrenholtz et al. 2015 entered production, the exclusion criteria has become better defined. In this Appendix, a third cohort of $N = 20$ are modeled and analyzed using the steady state model (SSM) and global optimization method described Chapter 5. The criteria for dataset exclusion in the $N = 20$ are the following, with the first being the most important:

1. **Does not reach steady state**

   The training of the steady state model kernel strongly depends on the MRTI datasets reaching steady state or at least being near steady state.

2. **Out of plane**

   If the long axis of the laser fiber is not in the MRTI imaging plane, the modeling assumption that the fiber is in plane is violated. With the MR data available, it is not possible to discern the precise azimuthal angle relative the MRTI imaging plane.

3. **The ablation is small**

   If the ablation is very small, i.e., $\sim 0.5\, \text{cm}$, with a laser power that should ablate a
considerably larger area, the MRTI dataset is not useful. This may occur because of exclusion criteria 1. and 2.

4. MRTI dataset is a test pulse

Before commencing the ablation in earnest, neurosurgeons check the laser’s position with a short test pulse — e.g., 4W for 30s. If a MRTI dataset is only a test pulse, it should be excluded.

5. MR artifact

If the MRTI dataset is severely obfuscated by image artifacts, it is not a useful dataset.

Table C.1 lists MRTI datasets that are excluded. Appendix A is an exhaustive listing of the MRTI datasets.

Table C.1: These ten datasets are excluded from the original 30 for reasons enumerated above in order to create the $N = 20$ cohort.

<table>
<thead>
<tr>
<th>Hash #</th>
<th>Exclusion criterion</th>
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<tbody>
<tr>
<td>0497</td>
<td>1. Does not reach steady state</td>
</tr>
<tr>
<td>0409</td>
<td>2. Test pulse</td>
</tr>
<tr>
<td>0415</td>
<td></td>
</tr>
<tr>
<td>0466</td>
<td></td>
</tr>
<tr>
<td>0468</td>
<td>3. Small ablation size</td>
</tr>
<tr>
<td>0471</td>
<td>4. Misses plane</td>
</tr>
<tr>
<td>0476</td>
<td></td>
</tr>
<tr>
<td>0447</td>
<td>4. Misses plane</td>
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<tr>
<td>0435</td>
<td>5. MR artifact</td>
</tr>
<tr>
<td>0440</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of optimization algorithms within LOOCV

The primary purpose of this Appendix is to present the results of the SSM in optimization and leave-one-out cross-validation (LOOCV) within a cohort more appropriate to the
Table C.2: This table lists datasets in the $N = 22$ cohort that there are included in Chapters 4 and 5 but excluded in Appendix C’s $N = 20$ cohort, and vice versa.

<table>
<thead>
<tr>
<th>Hash#</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0415</td>
<td>Included in $N = 22$ cohort</td>
</tr>
<tr>
<td>0435</td>
<td>Excluded in $N = 20$ cohort</td>
</tr>
<tr>
<td>0440</td>
<td>Excluded in $N = 22$ cohort</td>
</tr>
<tr>
<td>0447</td>
<td>Included in $N = 20$ cohort</td>
</tr>
<tr>
<td>0436</td>
<td>Excluded in $N = 22$ cohort</td>
</tr>
<tr>
<td>0457</td>
<td>Included in $N = 20$ cohort</td>
</tr>
</tbody>
</table>

SSM. However, a second opportunity for the Appendix is to juxtapose the subtly different LOOCV algorithms — the first from Section 4.3.5 and the second from Section 5.2.6. A key idea of LOOCV is that the parameter information that produces the best predictive results in training should be used to predict the ‘left out’ dataset within each iteration.

To the author’s interpretation, the gold standard LOOCV algorithm seeks to optimize the mutual performance among all training datasets. Emphatically, the optimization algorithm should seek to optimize the mean response function among all training datasets within a given LOOCV iteration. In Chapter 4’s methods, computational expenses render impractical the gold standard implementation of the LOOCV algorithm. Instead, Chapter 4’s method optimizes each dataset individually and averages the individually optimal parameters in order to predict the ‘left out’ case.

It is worth expounding upon the particulars of the computational costs associated with executing the gold standard LOOCV algorithm while using an optimization algorithm that minimizes a response/objective function. Firstly, the optimization algorithm’s objective function is an average of all training datasets. This requires the input parameter to be submitted to each training dataset to complete one iteration of the optimization. The optimization would then iterate and minimize the objective function. In Chapter 4’s case, the gradient-based optimization would submit a $\mu_{eff}$ value to 21 datasets and iterate to minimize the $L_2$ norm. Once minimization is complete, the optimal parameter value is tested on the ‘left out’ dataset, thus ending a single LOOCV iteration. The entire LOOCV
algorithm for Chapter 4 requires 22 LOOCV iterations with each iteration simultaneously optimizing 21 datasets. The second difficulty is that if ever the cohort is modified, the entire optimization must be repeated. In summary, in order to execute the gold standard LOOCV algorithm while using an optimization algorithm that minimizes an objective function, the resulting LOOCV algorithm is expensive in computational cost and inflexible regarding cohort modification. Chapter 4’s solution to this conundrum is to not execute the gold standard LOOCV and optimize individual datasets separately as a surrogate.

In Chapter 5, the result of global optimization is a vector map that represents an exhaustive list of every $\omega-\mu_{\text{eff}}$ pair and the resulting response function. Using the vector map, it is extremely simple to identify the input $\omega-\mu_{\text{eff}}$ that creates the optimal response function — see Section 5.2.6 for details. Chapter 5’s LOOCV method is able to relatively easily satisfy the ideal LOOCV algorithm. Furthermore, the vector map method can easily handle modifications to the cohort.

In order to investigate the difference between the gold standard LOOCV algorithm of Chapter 5 and the surrogate LOOCV algorithm of Chapter 4, this Appendix compares the two methods in Table C.5. The result is that the methods are very similar. It also suggests — but certainly does not guarantee — that using the surrogate LOOCV method with the FEM model is a close approximation of the gold standard LOOCV algorithm.
Table C.3: Here are the descriptive statistics for DSC performance during optimization and LOOCV for \(N = 20\) datasets. Steady state analysis using the 57°C isotherm damage model is denoted SS. “opt.” refers to optimization during the regular grid search; “Naïve” refers to the performance using literature values. 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 ascending ranked order.

<table>
<thead>
<tr>
<th>Descriptive Statistic</th>
<th>SS DSC opt.</th>
<th>SS DSC LOOCV</th>
<th>Naïve choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.74713</td>
<td>0.58552</td>
<td>0.45455</td>
</tr>
<tr>
<td>25%-ile</td>
<td>0.86899</td>
<td>0.77255</td>
<td>0.6068</td>
</tr>
<tr>
<td>Median</td>
<td>0.89973</td>
<td>0.85023</td>
<td>0.65639</td>
</tr>
<tr>
<td>75%-ile</td>
<td>0.91257</td>
<td>0.88146</td>
<td>0.76864</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.95307</td>
<td>0.93007</td>
<td>0.85749</td>
</tr>
<tr>
<td>DSC (\geq 0.7)</td>
<td>20</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td>0.88889</td>
<td>0.82359</td>
<td>0.66848</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.04680</td>
<td>0.088955</td>
<td>0.11479</td>
</tr>
<tr>
<td>Skewness</td>
<td>-1.3368</td>
<td>-1.0174</td>
<td>-0.23154</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>5.3510</td>
<td>3.634</td>
<td>2.2655</td>
</tr>
</tbody>
</table>

Table C.4: These percentiles correspond to several interesting DSC thresholds using the \(N = 20\) cohort. The “opt.” and “LOOCV” and “Naïve” columns refer to the same datasets described in Table C.3. 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.

<table>
<thead>
<tr>
<th>DSC threshold (Unity)</th>
<th>SS DSC opt. (%-ile)</th>
<th>SS DSC LOOCV (%-ile)</th>
<th>Naïve choice (%-ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>10.794</td>
</tr>
<tr>
<td>0.6</td>
<td>0</td>
<td>3.0939</td>
<td>23.351</td>
</tr>
<tr>
<td>0.7</td>
<td>0</td>
<td>6.6574</td>
<td>59.445</td>
</tr>
<tr>
<td>0.8</td>
<td>5.9200</td>
<td>35.067</td>
<td>89.333</td>
</tr>
<tr>
<td>0.85</td>
<td>13.314</td>
<td>51.541</td>
<td>95.934</td>
</tr>
<tr>
<td>0.9</td>
<td>50.513</td>
<td>81.819</td>
<td>100</td>
</tr>
<tr>
<td>0.95</td>
<td>94.678</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.975</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table C.5: The table compares the two LOOCV algorithms in the $N = 20$ cohort, described earlier. The “Parameter average” column refers to the LOOCV algorithm used with the FEM model; meanwhile, the “Vector map” column is the LOOCV algorithm outlined in Section 5.2.6. This Table’s “Vector map” column is also presented in Figure C.3 as the “SS DSC LOOCV”. 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 ascending ranked order.

<table>
<thead>
<tr>
<th>Descriptive Statistic</th>
<th>Parameter average</th>
<th>Vector map</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.6006</td>
<td>0.5855</td>
</tr>
<tr>
<td>25%-ile</td>
<td>0.7612</td>
<td>0.7726</td>
</tr>
<tr>
<td>Median</td>
<td>0.8230</td>
<td>0.8502</td>
</tr>
<tr>
<td>75%-ile</td>
<td>0.8787</td>
<td>0.8815</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.9113</td>
<td>0.9395</td>
</tr>
<tr>
<td>DSC $\geq 0.7$</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Mean</td>
<td>0.8059</td>
<td>0.8236</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.0893</td>
<td>0.0896</td>
</tr>
<tr>
<td>Skewness</td>
<td>-0.9101</td>
<td>-1.017</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>2.843</td>
<td>3.634</td>
</tr>
</tbody>
</table>
Figure C.1: For the $N = 20$ cohort, this Figure displays the simulated predictive performance of the regular grid optimization (in blue) versus a naïve literature value parameter choice (in green). A greater the area-under-the-curve (AUC), which is synonymous with the mean performance, indicates better performance.
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Vita

Samuel John Fahrenholtz was born on May Day 1987 to Randall Kevin Fahrenholtz, M.D., and Janice Faye Fahrenholtz in Kingman, Kansas. His two older sisters are Ashley Jo Angell and Cameron Beth Jeter, Ph.D. His entire primary and secondary education was in the Goddard Unified School District in Kansas. After graduating as the sole valedictorian of Goddard H.S. in 2005, Samuel matriculated in Kansas State University and sought a Bachelor of Science degree. He finished his physics B.Sc. in 2009 and began a doctor of philosophy degree in medical physics at The University of Texas M.D. Anderson Cancer Center in Houston, Texas. In 2010, Samuel married Monica Marie Frey, née.

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