Interdisciplinary Research (IDR) Origination Awards

Cover Page

Project Title

Accurate and efficient modeling for magnetic resonance-guided focused ultrasound treatment planning

Principal Investigator(s)

|  |  |  |
| --- | --- | --- |
| **Name** | **Department** | **College** |
| Christopher R. Dillon (PI) | Mechanical Engineering | Engineering |
| Steven P. Allen | Electrical and Computer Engineering | Engineering |
| David Dahl | Statistics | Physical and Mathematical Sciences |
| Christophe Giraud-Carrier | Computer Science | Physical and Mathematical Sciences |
| Britt Berrett | Healthcare Leadership Collaborative | Marriott School of Business |

Track

Track one

Abstract

Magnetic resonance-guided focused ultrasound (MRgFUS) is a knifeless technology that uses concentrated heat from sound waves to destroy diseased tissue. Due to its minimally invasive nature, the field is growing rapidly. MRgFUS, however, faces challenges of prolonged, expensive, and uncomfortable treatments. Poor understanding of treatment progression is a major cause of prolonged treatments. This proposal seeks to be better characterize the biomedical science and engineering of treatment progression of MRgFUS to improve treatment times and patient outcomes.

Currently, the surgeon’s experience and intuition inform most decisions affecting MRgFUS treatment duration. These decisions are made in a 24–to-48-hour treatment planning window. The surgeon must balance treatment aggressiveness with potential damage to nearby healthy tissues. Impromptu changes during the treatment are universal, and unexpected events regularly prolong the treatment.

Our team hypothesizes that computational models can improve treatment planning by augmenting the information available to the surgeon. The models would predict and, in turn, avoid problems that extend the treatment. We will test this hypothesis by building an accurate, rapid simulation framework to be executed by the surgical team.

Summary of Plans for External Funding

List target sources of external funding and proposed timeline for proposal submission.

**Project Narrative**

1. **Introduction to MRgFUS**

Magnetic resonance-guided focused ultrasound (MRgFUS) is a “knifeless” technology that heats and destroys diseased tissues deep within the body precisely and noninvasively. During MRgFUS, high frequency sound waves propagate from an external transducer, pass through intervening healthy tissue without harm, and focus inside a tumor or other diseased tissue (see Figure 1). The energy from the focused ultrasound waves quickly increases the local tissue temperature, which induces protein coagulation and necrosis (i.e, cell death) in a region the size of a large grain of rice. By moving the transducer or steering the ultrasound beam electronically, the entire tumor can be treated while minimizing damage to healthy tissues. To visualize the treatment, the focused ultrasound treatment is performed inside a magnetic resonance imaging (MRI) scanner. This magnetic resonance-guidance allows the performing clinician to observe the patient anatomy as well as the temperature changes being induced by the ultrasound in real-time. ADD REFERENCES

Focused ultrasound’s ability to non-invasively generate precise necrosis in deep tissues, with little impact on the surrounding structures, is unique. Both chemotherapy and radiation therapy have severe side effects that are not present with MRgFUS therapies. MRgFUS has no cumulative dose effects and can be repeated if necessary. The pain and recovery times for conventional surgery can last months, while patients treated with MRgFUS can return to regular life within a few days. Over the last two decades, the FDA has approved MRgFUS for the treatment of tremor-dominant Parkinson’s disease and essential tremor, uterine fibroids, benign and malignant prostate disease, bone metastases and osteoid osteomas. Hundreds of other indications are currently under investigation at various stages of preclinical and clinical trials (REF FUS foundation website).

While MRgFUS promises to destroy tumors with fewer side effects than traditional interventions, many patients experience multi-hour MRgFUS treatments. Long treatment times are not just inconvenient to the patient—they also correlate with adverse effects such as skin burns, incomplete tumor ablations, and unintended damage to surrounding healthy tissue. Reducing the duration of a given treatment improves patient outcomes, reduces the cost of the procedure, and increases the diversity of patients who can benefit from MRgFUS. This proposal seeks to address a major cause of prolonged MRgFUS treatment times: limited understanding of patient-specific treatment progression.

Do we want/need to focus on a specific indication to further motivate the story and narrow our scope? We could do breast cancer (collaborators at University of Utah starting MRgFUS breast clinical trial this month who’d be willing to share data, I’ve also got a student already segmenting breast MRI from UofU volunteers related to this), desmoid tumors (collaborators at Stanford University also willing to share data), other?

1. **Treatment planning- current approach**

In current practice, the surgeon’s experience and intuition inform most decisions (such as device positioning, transmission power, and acoustic pathway) that affect treatment duration. These decisions are made in a 24–to-48-hour treatment planning window and are based on pre-surgical MRI scans. The surgeon must balance the aggressiveness of the treatment and the benefits of destroying the entire tumor against the harms of damaging nearby healthy tissues. During the treatment planning phase, the surgeon effectively draws on her previous experience and training to mentally simulate the course of the surgery. The accuracy and relevance of these simulations are limited by a ~~host~~ plethora of patient-specific unknown factors. Regardless of the experience of the surgeon, impromptu changes to the treatment plan are universal and unexpected events almost always prolong the treatment.

1. **Model-based treatment planning- potential and challenges**

As an alternative to this clinician-centric approach, model-based treatment planning would use computational models of acoustic, temperature, and tissue-damage distributions to guide patient treatments. It could include optimization of the treatment path, heating duration and power-levels that will most effectively ablate the target tumor while sparing healthy tissues. Given the 24-to-48-hour treatment planning window, the thousands of computational scenarios necessary for treatment optimization would require extensive computational resources and/or necessitate that simulations be completed in seconds to minutes. High fidelity full-physics simulations of the acoustic, thermal, and tissue-damage fields in heterogeneous tissues are not likely to be executable in such time frames.

1. **Study Hypothesis**

Our team hypothesizes that model-based treatment planning can improve pre-surgical decision making by augmenting the extent and relevance of presurgical simulations. These models would predict and in turn avoid problems that would otherwise extend the course of treatment. We seek to test this hypothesis by building a MRgFUS simulation framework that can be executed by a member of the surgical team within a realistic time frame and with realistic accuracy.

1. **Study Methodology**

The study hypothesis presented above will be investigated in three specific aims with the initial goals of improving modeling accuracy for MRgFUS treatments, reducing the computational time and cost of those models, and assessing the appropriate product-market fit for our proposed model-based MRgFUS treatment planning platform.

**Aim 1:** Improve model accuracy. Develop models that account for (a) temperature-dependent tissue properties, (b) water-content weighted property distributions, and/or (c) quantification of model output uncertainty based on uncertainty of model inputs. Comparison with actual treatment data would be ideal.

**Rationale:**

**Experimental Methods:**

**Measures of Success:**

**Potential Problems and Alternative Strategies:**

**Aim 2:** Reduce computational time and cost. This will be accomplished through (a) improved code efficiency and parallelization, (b) implementation of machine learning algorithms, and/or (c) the creation and use of rapid surrogate/reduced-order models. After our initial discussions, we will likely be dropping (a) and (c) for this proposal and focusing on machine learning and specifically on the tissue segmentation process.

**Rationale:** One of the most time-consuming aspects of treatment modeling is the tissue segmentation process, in which MR images are used to identify and differentiate the various tissue types required for acoustic and thermal simulations. This process of separating skin, fat, muscle, bone, tumor, etc. involves tedious often hand-determined analysis of each two-dimensional image in the three-dimensional MRI (Figure here of segmented breast from Chloe: MRI, single slice and 3D projection). While software exists that semi-automates portions of the segmentation process (REF seg3D), cleanup of the segmented model is still required because multiple interrelated, case-specific imaging factors introduce variability and uncertainty. These imaging factors include, but are not limited to, MR image noise, physical proximity to the imaging coils, MR sequence sensitivity and contrast, and patient motion and respiration.

At end of section, include future directions/alternative applications for machine learning with MRgFUS: (1) Facilitate phase aberration correction (identifying timing delays of individual ultrasound elements that enable ultrasound waves to arrive at the target tissue synchronously and maximize heating). (2) Tie machine learning to model predictions themselves (acoustic, thermal, and tissue damage models) in a physics-informed machine learning approach.

**Experimental Methods:**

From David:

* 2(a) and 2(c) are up my alley (These are to be dropped from the proposal, but we can still do them. David’s help on aim 1 for model validation and uncertainty quantification will also be needed)
* Do you have any preliminary data and questions/concerns about the data? Is there something about your current data that is problematic?

From Christophe:

A few suggestions have already been made ("Initial ideas for how to use machine learning"). They all seem feasible, provided that data is available. Do we have access to segmented images labeled with the various tissue types for training? Or are you thinking of an unsupervised approach where we try to discover what various tissue types are present? Do we have access to data about phase aberration correction or timing delay data? It seems we would need patient data, including timing delays, outcomes, and other relevant information. Has anyone used these acoustic, thermal and/or tissue damage models? Would we be able to collect data about these for a variety of patients to build our models?  
  
I assume one can build models based on various physical properties of tissues, acoustic, pathways, etc. But if we wish to use machine learning, we do need access to a significant amount of quality data about patients, human decisions, actual outcomes, etc. Do we have access to such data?

**Measures of Success:**

**Potential Problems and Alternative Strategies:** Machine learning algorithms are only as good as the training data used to create them. Have radiologist confirm segmentation. Try unsupervised techniques. Remaining challenges of accelerating the acoustic and thermal models themselves (future work with machine learning or reduced order models).

**Aim 3:** Assess product-market fit. We will collect information from relevant stakeholders to identify the path of highest potential to clinical implementation of model-based treatment planning. Stakeholders include current clinicians performing treatments, companies developing hardware and software for MRgFUS, and staff engaged in the hospital workflow. We will identify data and visualization tools that will be most relevant and informative in developing treatments of highest efficacy and lowest cost.

**Rationale:**

From Britt: areas where he could contribute…

* Provide insight, perspectives, and connections
* explore funding for High Intensity Focused Ultrasound (HIFU) (in comparison to other modalities such as radiation therapy or proton beam)
* list/identify current commercial application of technology
* identify practitioners that might utilize HIFU

**Experimental Methods:**

**Measures of Success:**

**Potential Problems and Alternative Strategies:**

1. **Expected Project Outcomes**

**External funding proposals**: Completion of these three aims will provide the team with preliminary data necessary for a successful NIH R01 application to develop a model-based MRgFUS treatment planning platform.

**Conference presentations**:

**Scholarly articles** (Title, Journal, Lead Author):

**Student mentoring**:

**Scientific outcomes**:

1. **Study Schedule**

The study will be conducted according to the following schedule.

Table

Description automatically generated UPDATE FIGURE

1. **Study Team**

Two sentences per team member. One sentence highlighting expertise and experience. One sentence highlighting what they will do for this project.

Define each team members’ critical role and expertise, how they were integrated and essential for success

David Dahl is a Bayesian statistician with extensive experience collaborating with scientists in the life sciences. He will be particularly responsible for the statistical modeling of in Aim 1, but he will also support the machine learning in Aim 2 and the quantitative analysis for Aim 3.

**References**

**Study Budget (1 page)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Year 1** | **Year 2** | **Total** |
| Undergraduate Student Support (5) |  |  |  |
| Graduate Student Support (1) |  |  |  |
| MRI Scanner Usage |  |  |  |
| Subject Compensation |  |  |  |
| Supplies |  |  |  |
| **Total** |  |  |  |

**Budget Narrative**

what are you using the money for and why it’s a good use of funds

**Plans for External Funding (1 page)**

Chart or table: Funding agency, $ Amount, Years, Topic, Proposal submission date

* Make sure to emphasize plans for external funding, ID funds you’ll go after from Year 1 and then what you’ll target after Year 2

Submission of these grant proposals will follow the schedule below.

A screenshot of a graph

Description automatically generated with low confidenceNOTE MODIFY FIGURE

**Biographical sketches & Current and Pending Support**

**Biosketch: Dillon (2 pg limit)**

**Current and Pending Support: Dillon (**Title, source, and amount**)**

**Biosketch: Allen (2 pg limit)**

**Current and Pending Support: Allen**

**Biosketch: Dahl (2 pg limit)**

**Current and Pending Support: Dahl**

**Biosketch: Giraud-Carrier (2 pg limit)**

**Current and Pending Support: Giraud-Carrier**

**Biosketch: Berrett (2 pg limit)**

**Current and Pending Support: Berrett**