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 | BYU MRI Facility | Family Home and Social Sciences |
| David Dahl | Statistics | Physical and Mathematical Sciences |
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| Britt Berrett | Healthcare Leadership Collaborative | Marriott School of Business |

Track

Track one

Abstract

Magnetic resonance-guided focused ultrasound (MRgFUS) is a minimally invasive alternative to conventional breast cancer therapies that promises effective treatment with reduced side effects. Though the field of MRgFUS is growing rapidly, it faces challenges of prolonged, expensive, and uncomfortable treatments. This proposal seeks to be better characterize the biomedical science and engineering of treatment progression of MRgFUS to improve treatment times. 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.

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 and negatively impact patient outcomes. 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.

MRI facility seed grant

Focused Ultrasound Foundation?

NIH R21 or R15?

SBIR/STTR tech transfer grant?

**Project Narrative**

1. **The need for alternative breast cancer treatments**

Breast cancer is the most common cancer among women worldwide and the second most common cancer overall. In the United States, it is projected that over 287,000 women will be diagnosed with new cases of invasive breast cancer in 2022, and an estimated 43,250 women in the United States will die from breast cancer [1]. While the 5-year relative survival rate for breast cancer is high at approximately 90%, breast cancer and its treatment can have a profound effect on a person's physical, emotional, and mental well-being [2–4].

Breast cancer treatment side effects strongly impact a patient’s quality of life. Chemotherapy may cause fatigue, nausea, vomiting, hair loss, and cognitive impairment, especially in the first few weeks of treatment [5,6]. Hormonal therapy drugs can cause menopausal symptoms [5,7,8]. Surgery and radiation therapy can cause pain and soreness, with skin changes including redness, itching, and dryness [9–11]. These treatments also cause physical changes to the body, such as scarring and loss of sensation, that lead to body image issues and low self-esteem [10,12]. Generally, patients may experience feelings of fear, sadness, anxiety, and depression that can be compounded by physical changes and stress associated with treatment [4,13].

Clearly, new, less invasive treatments for breast cancer are needed, and many alternatives are being investigated and developed [14]. Magnetic resonance-guided focused ultrasound (MRgFUS) is one of these alternative therapies, with goals including both efficacious treatment and a reduction in the physical, mental, and emotional side effects associated with current standard treatments [15–18].

1. Diagram, venn diagram

   Description automatically generated**Introduction to MRgFUS**

MRgFUS is a “knifeless” technology that heats and destroys diseased tissues deep within the body precisely and noninvasively [19]. During MRgFUS, high frequency sound waves propagate from an external transducer, pass through a coupling water bath and intervening healthy tissues 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 [20,21]. By moving the transducer or steering the ultrasound beam electronically, the entire tumor can be treated while minimizing damage to healthy tissues. To enable monitoring of 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 caused by the focused ultrasound in real-time [22–24].

Figure 1: Schematic of MRgFUS treatment. MRgFUS can noninvasively heat and destroy diseased tissues with high precision.

Focused ultrasound’s ability to non-invasively generate precise necrosis in deep tissues, with little impact on the surrounding structures, is unique. The severe side effects of chemo- and radiation therapy 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. For breast cancer patients, MRgFUS is an especially attractive alternative for those who desire breast conserving therapy, since it is completely non-invasive and could significantly improve cosmetic outcomes compared to surgery. 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 [25]. Hundreds of other indications are currently under investigation at various stages of preclinical and clinical trials [25].

1. **MRgFUS treatment planning- current approach**

While MRgFUS promises to destroy tumors with fewer side effects than traditional interventions, many patients experience multi-hour MRgFUS treatments [REFS]. 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 [REFS]. **This proposal seeks to address a major cause of prolonged MRgFUS treatment times: limited understanding of patient-specific treatment progression.**

The surgeon uses a 48-hour pre-surgical treatment planning window to make decisions that have critical consequences for the patient. However, in current practice, the surgeon relies almost entirely on previous experience and intuition to make these decisions. When the patient’s anatomy and pathology extend beyond the surgeon’s realm of experience, the treatment becomes suboptimal. For example, the position and orientation of the MRgFUS transducer relative to the patient’s anatomy plays a critical role in how quickly the diseased tumor reaches a lethal temperature. Bone, gas pockets, and even large packets of adipose tissue disrupt ultrasound transmission. For a complex tissue such as the breast, it is nearly impossible for a human to predict the complex ultrasound propagation patterns from the dozens to hundreds of possible applicator orientations. A misorientation, however, may introduce burns to the skin or other sensitive, healthy tissues or prevent full ablation of the target, diseased tissue [Skin burn refs].

A second critical decision is the determination of the treatment path, including where to start the treatment and how it should progress to fully destroy the tumor. Excessive time in one orientation can lead to slow but damaging thermal exposures to healthy tissues in the ultrasound beam path. However, reorienting the transducer or patient takes additional time with no guarantee of improved treatment outcomes. In short, 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 within a complex system with many variables and degrees of freedom. During the treatment planning phase, the surgeon effectively draws on her previous experience and training to mentally simulate the course of the surgery. 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- a potential solution with 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 would 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**

An initial investigation of the study hypothesis presented above will be performed in three specific aims to 1) improve modeling accuracy for MRgFUS treatments, 2) reduce the computational time and cost of those models, and 3) assess the appropriate product-market fit for our proposed treatment planning platform within the US healthcare system. While these aims are insufficient to fully investigate the study hypothesis, they will provide sufficient preliminary data and research momentum for our planned external funding proposals, in which we will more extensively explore model-based treatment planning’s challenges and opportunities.

**Aim 1:** Improve predictive model accuracy for breast cancer MRgFUS treatments. Develop models that include (a) temperature-dependent tissue properties, (b) water-content weighted property distributions, and (c) quantification of model output uncertainty based on uncertainty of model inputs. Comparison with actual treatment data from breast MRgFUS clinical trials at the University of Utah will provide evidence for model validation.

**Rationale:** Improved and clinically validated MRgFUS models are essential for the widespread adoption of model-based treatment planning. Most current MRgFUS models utilize the Pennes bioheat equation to predict how thermal energy from the focused ultrasound heats up the tissue and then dissipates through the tissues [26]. Unfortunately, those simulations consistently overpredict temperatures at the target tissue and regularly underpredict heating at other locations (REFS). Without the ability to accurately predict temperature changes, confidence in the models is limited. For that reason, model-based treatment planning has not been widely used in the clinical setting.

By developing models with fewer simplifying assumptions, the accuracy of model predictions should improve. Most models utilize a limited number of tissue types and constant, uniform properties within each tissue type. However, the reality of tissue distributions and property variations is much more complex. For example, many tissue properties vary with temperature (REFS) and with the extent of treatment (REFS). Mild heating will induce vasodilation and dynamically increased blood flow, which will carry away thermal energy (REF). In many tissues, including the breast, the transition between tissue types (such as fat and fibroglandular tissue) is gradual rather than abrupt, so classifying tissue into coarse bins removes refinement in the model.

**Experimental Methods:** We propose to improve MRgFUS predictive models with two methods that reduce the number of simplifying assumptions and with one method that explicitly accounts for uncertainty in the model inputs. **Method 1**- We will extend current models of acoustic power deposition and the Pennes bioheat equation to account for temperature-dependent tissue properties found in the scientific literature (REFS). The acoustic properties will be updated periodically (based on time- or temperature-thresholds yet to be determined) for improved power deposition predictions. Thermal properties will be dynamically updated in a finite-difference time-domain solver as local tissue temperatures change. **Method 2**-Instead of applying the traditional modeling approach of segmenting tissue types into limited bins with constant, uniform properties, we propose to develop models with a spectrum of properties weighted by the MRI-quantified water content of the tissue. Tissue properties based on water content are available in the literature (REFS). This method will capture the gradual transition between tissue types and potentially enable more accurate temperature prediction. **Method 3**-There are many uncertain model inputs introducing potential errors into MRgFUS predictions. This method seeks to quantify that model uncertainty rather than ignore it. Using the range and anticipated distribution of each property rather than a single expected value, the full possibilities of MRgFUS model predictions can be explored and characterized statistically rather than relying on a single anticipated predictive scenario.

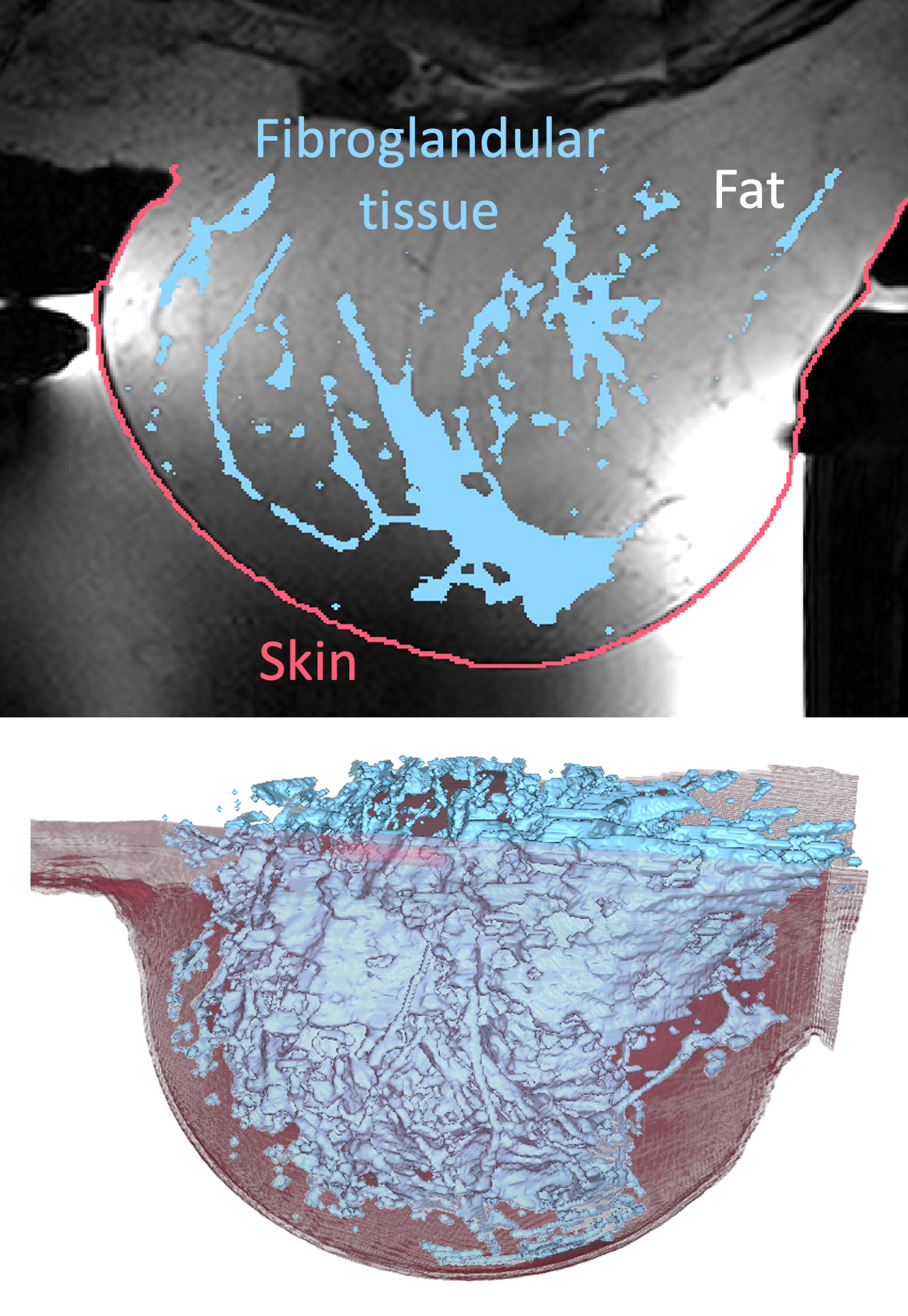
**Measures of Success:** To evaluate model improvement, the temperatures achieved during clinical MRgFUS treatments of breast cancer being performed by collaborators at the University of Utah will be retrospectively predicted using each of the above methods in addition to the traditional modeling approach. The University of Utah will provide de-identified MRI data from before, during, and after the treatment, as well as information including transducer positioning, ultrasound power and duration, time between heating, etc. WHAT KIND OF STATISTICAL METHOD WOULD WE USE HERE TO CHARACTERIZE MODEL ACCURACY? These validation efforts will demonstrate the accuracy of our methods and increase confidence in the usefulness of model-based treatment planning.

What more general measures of success might we include? Number of treatments successfully modeled? Papers? Preliminary data for future grants? Mentoring of students? Should we leave this for the Expected Project Outcomes section?

**Potential Problems and Alternative Strategies:** Property values and distributions in the scientific literature may not cover all desired tissue types. Dr Dillon’s research lab is developing the capability to measure temperature-dependent acoustic and thermal properties including tissue absorption, speed of sound, thermal conductivity, thermal diffusivity, and specific heat capacity. If necessary, tissue samples of bovine or porcine skin, fat, muscle, or glandular tissue acquired from local slaughterhouses can be characterized and utilized in our models. OTHER?

Calibrating models to actual treatment or experimental data would seems to be essential, not just ideal. These models could be a physical / engineering model whose parameters we estimate using treatment or experimental data. Or, these could be statistical models designed to summarizing the relationships among the variables. Which of the two were to thinking about here?

I suggest we describe what specific data we think we can get (from UofU or Stanford) or what data we plan to collect. We can then describe what we will do this this data. For this, we need to decide if are we are: 1. estimating the parameters in a physical model or 2. using a statistical model to describe relationships? Either is fine, but details of the anticipated data would help us in developing this section.

**Aim 2:** Reduce the computational time and cost to prepare and utilize predictive models for breast cancer MRgFUS treatments. This aim will address one of the most time-consuming portions of treatment modeling: the tissue segmentation process. We propose to reduce segmentation time by (a) developing a library of segmented breast models, (b) improving and confirming segmentation accuracy through iterative discussion and training with a clinical radiologist, and (c) using the library of segmented models to train a machine learning algorithm how to perform tissue segmentation.

**Rationale:** Given the 24-to-48-hour treatment planning window, the time required to perform MRgFUS treatment predictions must be reduced from hours to minutes. If such time reductions can be accomplished without sacrificing model prediction accuracy, thousands of unique treatment scenarios and plans could be evaluated to inform the surgeon of the most optimal treatment plan.

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 (an example of a segmented breast model is shown in Figure 2). 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. The segmented breast model shown in Figure 2 required 40 hours of time from one BYU graduate student.

Figure 2: (Top) Single 2D slice of segmented breast model overlayed on MRI scan. (Bottom) 3D projection of the segmented breast model.

**Experimental Methods: Creating the library**-The clinical pretreatment MRI data described for use in Aim 1 will form the foundation of our segmentation training library. Undergraduate students will be trained to interpret the MR anatomical images, in the use of segmentation software, and in model cleanup best practices. They will segment a model for each clinical patient that can be used for Aim 1 and Aim 2. The library will expanded by enrolling female volunteers for anatomic breast imaging at the BYU MRI facility with IRB approval. The MRI parameters used for these scans will mimic those of clinical imaging protocols as closely as possible. The imaging datasets will be deidentified and also segmented to expand the segmentation training library. **Evaluating the library**- After a set of five anatomic segmented models have been generated, a clinical radiologist at the University of Utah will be enlisted to evaluate the accuracy of the segmentation. Training and feedback from the radiologist will be used to correct segmentation errors and to prevent similar problems in the segmentation of future datasets. It is anticipated that a full library of XX segmented models will be required to complete the segmentation training library. **Training the machine learning algorithm**- Once the library has been created and confirmed accurate, 80% of the MR imaging datasets and corresponding segmented models will be used to train a machine learning algorithm to perform the segmentation. The remaining 20% of the data will be used to validate the accuracy of the machine learning-generated segmented models. What metrics are used for this?

**Measures of Success:** Segmentation accuracy, of the library and machine learning results, will be evaluated by a clinical radiologist at the University of Utah. The development of the segmented models will be a valuable contribution, even without the machine-learning algorithm. The models will be used for retrospective analysis in Aim 1 and as part of treatment outcome studies for the University of Utah clinical trial. The development of a rapid segmentation protocol that uses machine learning will shorten the modeling timeline dramatically and will be foundational to our eventual goal of building a model-based treatment planning platform for MRgFUS thermal therapies.

What other measures of success might we include? Papers? Preliminary data for future grants? Mentoring/experiential learning opportunities for students?

**Potential Problems and Alternative Strategies:** Machine learning algorithms are only as good as the training data used to create them. If we determine that our student-produced segmented models lack sufficient accuracy or if we cannot collect sufficient patient and volunteer data for training, we may investigate the use of unsupervised machine learning techniques for tissue segmentation [REF]. Reducing segmentation time will reduce MRgFUS predictive model computation times, but the challenge of slow acoustic and thermal models themselves will remain. Future efforts could include the use of physics-informed machine learning algorithms or reduced order models to accelerate predictive simulations.

**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 (R15) 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

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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

**Christopher R. Dillon** is a mechanical and biomedical engineer with over a decade of experience in acoustic and biothermal modeling of MRgFUS therapies. He will oversee the project generally, coordinating between co-investigators at BYU and collaborators at the University of Utah, and specifically mentor students in the development of improved predictive models for Aim 1. **David Dahl** is a Bayesian statistician with extensive experience collaborating with scientists in the life sciences. He will be particularly responsible for the statistical uncertainty modeling in Aim 1, but he will also support the machine learning assessment in Aim 2 and the quantitative analysis for Aim 3.

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**Study Budget (1 page)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Year 1** | **Year 2** | **Total** |
| Undergraduate Student Support (10) | **12000** | **12000** | **24000** |
| Graduate Student Support (3.5) | **36000** | **46000** | **82000** |
| MRI Scanner Usage | **8000** | **0** | **8000** |
| Subject Compensation | **2000** | **0** | **2000** |
| Supplies | **2000** | **2000** | **4000** |
| **Total** | **60000** | **60000** | **120000** |

**Budget Narrative**

A total of **$120,000** is requested over the two-year period of this proposal. Of this amount, a total of **$82,000** is requested to support three graduate students (mentored by Drs. Dillon, Dahl, and Porter, respectively) who will perform, respectively, Aims 1.1, 1.2, and 2. Dr. Dillon’s student will be engaged in Aim 1. An additional $10,000 is budget in year 2 for part time support for an additional student in Dr. Berrets’s lab to conduct with the market study described in Aim 3. A total of **$24,000** is requested over both years to support up to 10 undergraduate students to undertake the laborious process of segmenting MR images acquired in Aim 1, conduct subject recruitment, and acquire MR images. A total of **$8,000** is requested to support 40 MRI scans of recruited subjects plus 8 pilot scans that will be used to ensure proper data collection. Our team will pursue and MRI Research Facility Seed Grant to fund an additional $8000 of scanning to supplement the study. A total of **$2,000** is requested for subject compensation. Finally, a total of **$4,000** is requested to purchase supplies, such as tissue sample, test equipment, supercomputer time, and purchasing market research as described in Aims 1-3.

**David:** I could use funding for a statistics student to help clean, manage, and analyze the data. This could be as much as $8,000 a year, but it may be much less and not all the years. If the budget is tight, I can pay the student from other sources.

**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

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**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**