Part I

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2.1 Objectives

The concept of simulation in the context of the CIBC is the prediction of the behavior of cells, tissues, and organs under simplifying assumptions over known anatomical domains in response to pre-determined boundary or initial conditions. Thus the overall goal of the CIBC is to provide biomedical scientists with access to comprehensive and sophisticated software tools with which to define the assumptions, the domain, and the initial or boundary conditions and then to carry out simulations using advanced and robust numerical and computation algorithms. No single group or center can support the vast breadth of possible simulation types and the CIBC will continue to focus on the core domain expertise of multiscale modeling of the electrical activity in the body, both intrinsic activity from excitable cells in, for example, the heart and nervous system, as well as extrinsically applied electric fields used to stimulate activity in the body.

The majority of the proposed DBPs make use of simulation to predict bioelectric activity and the needs of the scientists and engineers in those DBPs will continue to drive the specific development of software within the simulation TRD. There are DBPs that seek to simulate intrinsic cardiac excitability starting with the cell and extending to the behavior of the entire heart. There are DBPs that seek to seek means of representing electrical activity in the brain in forms that can generate the electric potentials on the scalp and the magnetic fields outside the head. There are also DBPs that attempt to influence the behavior of tissues and organs under the influence of applied electrical fields, behaviors as diverse as defibrillation of a heart that has fallen into fatal, uncontrolled, electrical spasm and the stimulation of bone growth into the surface textures of metallic implants in patients who have lost limbs to injury or accident.

Simulation also plays a major role in the integrated view of subject specific modeling that is the unifying goal of the entire CIBC. The pipeline that starts with image data and then seeks to diagnose and monitor patients often includes components of simulation that depend on accurate and subject specific geometric models of the anatomy to predict normal and pathologic behavior. The specific simulation components we will develop also represent the integration of the clinical needs of the DBPs with the skills and knowledge base of researchers at the SCI Institute and CVRTI who will participate.

Parallel to other TRDs, there are three broader objectives form which emerge the specific aims of this proposal. The first objective is to provide a set of software tools for constructing and executing simulations related mostly but not exclusively to bioelectric fields in the body. The second is to make these software tools available to technical scientists and engineers in a structure that is flexible, portable, and extensible enough to allow them to not only use existing tools but to effectively develop new ones based on their own expertise and novel ideas. The third major objective is to make the integrated set of tools developed both within the SCI Institute and from external experts available in a way that is biomedically intuitive and application specific so that clinicians and biomedical scientists can also benefit from them and accelerate their own research and/or improve the level of care available to patients.

From these goals and objectives have come the following specific aims that will be the immediate focus of technical research and development within the CIBC:

1. Simulation of multiscale intrinsic bioelectric activity. We will continue to develop and expand capabilities for simulating electrical activity at the membrane, cellular, tissue, and whole organ levels for both the heart and nervous system. A special area of focus will be novel electric source formulations that not
only capture essentials of the electric fields generated from tissues but also form the basis of associated estimation formulations described in Section ??.

2. Simulation of the application of external electric fields to living tissues. Electric fields are applied by devices in a growing range of settings and we will expand our ability to simulate the interactions of the applied fields with heart tissue, the brain, skeletal muscle, and even bone in order to improve and optimize the clinical use of stimulation devices.

3. Development and implementation of portable, robust software for efficient numerical solution approaches. The complexity of living systems exceeds the capacity of all computers so that biomedical simulation must include both appropriate simplifications of the problem formulation as well as efficient numerical and computational approaches. We will continue to identify novel means of improving the efficiency of simulations relevant to the Center with specific focus on the use of streaming architectures and GPU based computing.

4. Validation and parameter sensitivity analysis. Truly comprehensive, gold-standard data are rarely available for testing of simulation results so that other approaches are necessary for validation. We will continue research projects seeking to develop numerical approaches to validation with special focus on the study of parameter sensitivity and make these and other techniques available to biomedical scientists.

5. Curation of open source samples of geometric models, measured behavioral data, and simulation results for evaluation and comparison of simulation approaches. Shared, documented, and representative data sets in suitable numbers offer a means of objective comparison of simulation approaches that is rarely available to scientists. Our close collaboration with outstanding scientists and physicians as well as extensive internal experience in experiments will allow the CIBC to expand the availability of such data sets for use within the Center and in the larger simulation community.

2.2 Rationale

There is a natural synergy between simulation and computing that has been and remains a core element of the goals and progress of the CIBC. Although computer based simulation has a relatively modern history, the basic elements of simulation are as old as mathematics. Predicting the trajectory of a cannon ball or the pathways of the planets both make use of the essential elements of simulation: mathematical equations that describe behavior and a means to solve those equations under realistic conditions. The need to solve equations that are complex enough to predict behavior has further ensured that progress in simulation has been linked to advances in numerical mathematics and calculation and, in recent years, to the dramatic improvements in computers. While raw computing power is essential for the use of advanced simulation, the access to that power comes through the software, which implements the descriptive equations of a system and provides the interface to parameters and data to drive the simulations and to the display and analysis of the results.

2.2.1 Role of Simulation in Biomedicine

One of the first modern examples of simulation leading to breakthroughs in our understanding of physiology came in the 1950's when Hodgkin and Huxley used simulation of ionic currents and membrane voltages in nerve axons to derive fundamental ideas about the transport of ions and cellular electrophysiology.1–4 The results from these studies included a Nobel Prize and a formalism that was only later confirmed through structural and functional studies of membrane channels. A modern example of simulation providing fundamental insight came 10 years ago when Clancy and Rudy first described a modification to the Hodgkin-Huxley formalism that allowed them to incorporate the stochastic behavior of the sodium channel in both wild-type and diseased conformations.5 By means of their simulation models, it was possible to link the role of genetic abnormality with functional consequences in a highly quantitative manner, a feat that would not have been possible without computer simulation.

In the past 50 years, there has been a close parallel advancement of simulation and computing performance to the point that virtually any biological system can have a simulation counterpart—although simplifications are always required to formulate a tractable simulation. There is a clear trend toward incorporating simulation into
Successful comparison suggests that the model might, indeed, be adequate, i.e., simulation model provides a means of testing these relationships by including explicitly all the factors that the
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that surrounds the heart, and the location of the recording electrodes. Thus, the relationship between a change
signal is the integration of such factors as the bioelectric source, the size and shape of the volume conductor
For example, the electrocardiogram (ECG) measured on the body surface is easily measurable, however, this
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forward problems are therefore simulation problems that describe, for example, potentials on the body surface
in that many estimation problems can be expressed as solving a simulation problem in reverse. Bioelectric
other system constraints. For example, one often wishes to estimate the location and strength of bioelectric
the physiological or pathophysiological responses of a system based on measurements of that response and
more interesting for biomedicine as it seeks to determine, for example, the values of parameters that determine
reconstruct more finely resolved image or signal from widely spaced measurement sites. The first situation is the
response or of a subset of parameters. A simple example of the second situation is interpolation, which seeks to
recover or uncover the values of system parameters from measurements of either the integrated system
model provides a means of testing these relationships by including explicitly all the factors that the
designer of that model considers essential. A crucial step then becomes comparing the results of the model
results of actual measurements, under varying states of the underlying model components and parameters.
Successful comparison suggests that the model might, indeed, be adequate, i.e., the investigator has made cor-
correct assumptions about which parameters are relevant and how each parameter affects the integrated system.
A failure to achieve agreement between simulation and measurement indicates that parameters, or their effects,
are missing and may even suggest which additional features are necessary to create a useful simulation model.
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ultimately the communication among members of a population. Whole organ simulations seek, for example, to
to predict overall behavior based on rates of flux and the effects of external neural and hormonal influence. At the
highest scale are numerous models that seek to simulate interactions among a set of physiological systems and
predict, for example, the role of autonomous regulation of blood pressure under the influence of anesthetics.12

Simulation can and does play numerous roles in the current pursuit of biomedical research and clinical
practice. Probably its most often cited advantage is the ability of a simulation to carry out measurements or
in silico experiments or clincial diagnoses that are either impossible, impractical, or unethical in actual living
organisms. However, creating models that have been suitably validated and verified to the point at which they
generate reliable results for this type of application is a significant challenge, especially when they are applied
to situations involving pathophysiology or abnormal structure. This need for robust verification is even more
obvious and pronounced in the case of simulations applied to human patients, although simulations would
almost never be the sole source of diagnostic information applied to the actual treatment of patients. Examples
of such clinical simulations include the use of pharmacodynamic and pharmacokinetic models of anesthetic
drugs to guide the application of such drugs in patients12 or the prediction of bioelectric potentials on the inner
chambers of the heart from measurements of potentials in the blood volume, the biophysical basis of the highly
successful clinical cardiac mapping system known as EnSite.13,14

A more basic science application of simulation is to create numerical models of integrated behavior that is
observable in experiments as a complete system, but whose constitutive elements are not directly available.
For example, the electrocardiogram (ECG) measured on the body surface is easily measurable, however, this
signal is the integration of such factors as the bioelectric source, the size and shape of the volume conductor
that surrounds the heart, and the location of the recording electrodes. Thus, the relationship between a change
in any single parameter and the possible resulting changes in the ECG are complex or even non-unique. A
simulation model provides a means of testing these relationships by including explicitly all the factors that the
designer of that model considers essential. A crucial step then becomes comparing the results of the model
with results of actual measurements, under varying states of the underlying model components and parameters.
Successful comparison suggests that the model might, indeed, be adequate, i.e., the investigator has made cor-
correct assumptions about which parameters are relevant and how each parameter affects the integrated system.
A failure to achieve agreement between simulation and measurement indicates that parameters, or their effects,
are missing and may even suggest which additional features are necessary to create a useful simulation model.
It is in this domain of integrating multiple factors that simulation can play a unique and essential role to the
understanding of complex systems. There are limits to the number of parameters and the complexity of their
interactions that any human can integrate mentally so that a quantitative simulation model becomes an essential
tool to include all the interactions necessary to explain even moderately complex physiological mechanisms.

A final aspect of simulation that we have separated for special emphasis in this proposal is that of estimation
(see Section ??). Estimation differs from simulation as we define it here, in that estimation typically seeks to
recover or uncover the values of system parameters from measurements of either the integrated system
response or of a subset of parameters. A simple example of the second situation is interpolation, which seeks to
reconstruct more finely resolved image or signal from widely spaced measurement sites. The first situation is the
more interesting for biomedicine as it seeks to determine, for example, the values of parameters that determine
the physiological or pathophysiological responses of a system based on measurements of that response and
other system constraints. For example, one often wishes to estimate the location and strength of bioelectric
sources in the brain from measurements of the electric potentials on the scalp or the magnetic field outside the
head. Simulation, on the other hand, usually assumes sufficient knowledge of the underlying system parameters
and the goal is to predict the system response. There is a natural synergy between simulation and estimation in
that many estimation problems can be expressed as solving a simulation problem in reverse. Bioelectric
forward problems are therefore simulation problems that describe, for example, potentials on the body surface
from known cardiac or brain sources. The associated inverse problems are than estimation problems that seek

to recover the source parameters from measurements of body surface potentials. In practice, the solution to estimation problems often involves either inverting or iterative re-solving (with adjusted source parameters) of an associated simulation problem.

This close relationship between estimation and simulation in the CIBC also drives some of the specific research and the DBPs related to both TRDs. The use of simulation in the context of cardiac defibrillation is typically restricted to predicting the outcome of a given electrode location and stimulation strength combination for a specific torso geometry (see the Simulation of Cardiac Defibrillation DBP in Section ?? for details). We propose also to address this application in the context of estimation, to first establish adequate criteria for successful defibrillation based on electric field strength achieved at the heart and then estimate the electrode locations and stimulation strengths that will achieve those criteria. In a similar way, we will develop a DBP around an ongoing research project aimed at accelerating bone growth by simulating electric field around the boundaries of a metallic implant in the residual bones of amputees (see the Simulation of Electric Stimulation for Bone Growth DBP in Section 3.2 for details). The first step is to complete and validate a suitable simulation approach to simulate the electric field from given stimulation electrode locations and voltage for a patient specific model of the limb. The associated estimation step will then be to start with a desired electric field distribution over the bone implant and then estimate the best stimulation electrode locations and voltage. A third DBP with this same flavor seeks to identify the location and amplitude of current dipole sources in the brain from scalp potentials or external magnetic fields (see the Brain Source Localization DBP in Section ?? for details). The simulation problem is to predict the external electric potentials and magnetic fields from known bioelectric source configurations and patient specific models of the head. The associated estimation problem is then to identify the sources based on knowledge of the head geometry and the measured electric potentials or magnetic fields.

In each of these (and other) simulation problems, a substantial secondary goal will be to develop models that are highly efficient or lend themselves to inversion so that we can solve the associated inverse problem. Efficiency is required because often estimation techniques involve many (sometimes even thousands of) repetitions of the simulation, each with different parameters; thus even modest improvements in the simulation can result in dramatic improvements in estimation time. In other cases, the simulation formulation must be invertible in some mathematical sense. To be useful for estimation, this inversion should lead to unique answers, i.e., each set of boundary conditions or measurements should lead unambiguously to a source model. In some cases, unique inversion is theoretically possible but may not be numerically stable because the resulting problem is physically ill posed and the resulting simulation ill conditioned. Thus a goal throughout this TRD will be to formulate simulation approaches that not only solve the initial problem posed as a simulation but to formulate them, wherever possible, in a way that permits an associated estimation formulation.

2.2.2 State of Simulation Software

As a sub-discipline of scientific research, biomedical simulation places unique demands on computing, as there is simply no practical way to carry out mathematical modeling of biomedical behavior without sophisticated software. By contrast, in principle, a scientist can still collect, process, and even visualize measurement results without a computer using existing hardware and manual processes. In simulation, only the most trivial models, based upon the most simplified geometries, can be carried out without the use of computing. In fact, the complexity of biological organization and function is such that even today, simulating almost any reasonably-sized biological system taxes the largest computers and the most efficient software. For example, there are simulations of heart electrophysiology that have included 25 million points and the most recent even 125 million points.

A recent summary of the state of the art in models of cardiac function carried out by an invited panel of internal experts under the auspices of the NHLBI includes the following recommendations regarding the need for improvements in computing support for cardiac simulation:

Support the development and experimental validation of integrative multiscale computational models of the normal human heart and of specific cardiac diseases (arrhythmias, heart failure, and myocardial ischemia/infarction) and their progression that:

- Integrate multiple subsystems specific to the pathogenesis of the disease state and characterize the dynamics of their interactions at each scale. This will also require support to develop
and maintain advanced computational tools and technologies needed to ensure computational tractability and robust and efficient models of human electromechanical activity.

- Incorporate the structural alterations associated with specific diseases at each scale.
- Characterize the adaptive and maladaptive responses that underlie the progression of disease.
- Integrate across scales to predict the electromechanical outcomes of genetically based and acquired perturbations.
- Inform clinical diagnosis and guide the selection of appropriate therapies in a patient-specific manner. Molecular/cellular investigations of explanted tissues, including histological and/or immunohistochemical characterization, should be combined with clinical data and high-resolution, noninvasive structural (computed tomography, magnetic resonance imaging), functional (echocardiography), and electrophysiological imaging obtained before surgery.

The themes of these cardiac-specific recommendations carry over into other application areas and form the basis of many of the specific aims of this proposal and the CIBC. Specifically we propose to address the incorporation of pathophysiology into models that span a range of scales; the creation of robust, efficient software to implement tractable models; the need to incorporate structure in a subject specific manner; and the inclusion of advanced imaging as the basis for translation to the clinical setting.

No single group can pursue the full range of simulation opportunities in biomedicine and no single software infrastructure is suitable for all types of simulation. As a Center, we have established expertise in the area of simulation in bioelectric fields, have built on and expanded that expertise in the current funding period, and propose to continue to make this form of simulation a centerpiece of our future research activities. At the start of the Center, our focus was on passive electrical characteristics of the torso and head and their response to endogenous bioelectric sources (the heart and brain); we solved both forward problems based on known sources as well as inverse problems, in which we sought to identify and localize bioelectric sources from measurements on (or outside) the body surface. In the past funding period, we extended simulation from the passive to the active aspects of bioelectric, to describe the function of the excitable tissues in the body. We also extended the use of bioelectric fields to incorporate applying external electric fields to tissues of the body, for example, defibrillation of the heart, deep brain stimulation, and the acceleration of bone growth under the influence of electric fields.

2.2.3 Future vision

We propose to continue to grow and expand all aspects of the Center’s activities and to increase the impact of our research in simulation software by adding more DBPs (which are referred to as “Principle Collaborators” in our current structure). We will also continue to expand the application domain to cover more examples of bioelectrics in biomedicine, projects we have recently begun in, for example the area of stimulation of bone growth. We will also seek to develop approaches and software that will provide for subject specific simulation that is a necessary step in the path to translating the concepts of physics and physiology to the clinical domain. Most of our proposed DBPs are clinical in their goals and some will include the use of our software in clinical settings to improve patient monitoring and care. Simulation will be a key component to many of these projects and we will continue to innovate in our use of simulation.

We will achieve these goals through a balanced approach to software development. We will continue to create new algorithms and numerical approaches as necessary and also to incorporate the progress of other groups wherever possible and sensible. As with all the TRDs, we will leverage the outstanding original research emerging from the SCI Institute and the CVRTI and seek to make the fruits of that research available to biomedical scientists through our software infrastructure. We will also use a balanced software infrastructure that includes our integrated problem solving environment, SCIRun, and its biomedical elements, BioPSE, and also includes standalone applications that have focused purpose, small footprint, and application specific user interfaces. Of special important in the use of simulation, we will strive to implement or incorporate efficient numerical approaches that allow not only for more rapid simulation but facilitate the transition from simulation to estimation, a key step in the goal of translation to clinical practice. One path to achieving such increases in efficiency will be by means of “streaming architectures” implemented on graphical processing units (GPUs) in what is termed general purpose computation on GPUs (GPGPU). The original purpose of GPUs was to accelerate the computations specific to graphical rendering and display but many of those same tasks are common to general purpose numerical algorithms. Thus it is possible to implement these algorithms in a form that can run on
the GPU, achieving dramatic improvements in performance because the GPUs are highly parallel in structure and can calculate at teraflop speeds.

This TRD shares with this entire proposal a rationale based on recent and emerging breakthroughs in technology and in medicine. The opportunities represented by GPGPU computing are just one such example as the capacity and efficiency of computing hardware generally continues to outpace the software that is necessary to take advantage of it. Even desktop computers rarely consume all available resources and specialized graphics cards also offer new opportunities for interactive visualization that are rarely supported by current software. By being housed in a setting such as the SCI Institute, the CIBC can continue to benefit enormously from an environment that continues to lead in research related to scientific computing. We are able to identify new technologies as they emerge and translate them into tools that can benefit biomedical research and clinical practice. Section ?? describes the facilities and resource in more detail, the key element here being that simulation research and development in the CIBC will continue to represent the state of the art, as will the software what we develop to implement that state of the art.

A second facet of the Center that will ensure both the high technical level and, more importantly, the relevance of the simulation research we propose is the close affiliation through DBPs with outstanding leaders in biomedicine and clinical practice. The ongoing project with Dr. John Triedman on the simulation of ventricular defibrillation in pediatric cardiology has recently expanded to include clinical collaborators from the University of Utah, experts in the use of implantable devices for control of life threatening arrhythmias who will drive the research to ensure high utility for the understanding and optimization of device implantation and adjustment. Developments in this collaboration have also spawned a new collaboration and a DBP with Dr. Natalia Trayanova, a world leader in the use of the simulation of fibrillation and defibrillation and the first to carry out such simulations on high resolution models of the whole heart. In another new DBP, we will collaborate with Dr. Nassir Marrouche, a clinical electrophysiologist with enormous success in the field of atrial arrhythmias. Dr. Marrouche leads a highly interdisciplinary group of physicians, biomedical engineers, and image and image processing specialists from academia and industry who are using imaging, simulation, and visualization to advance the management and treatment of atrial fibrillation. Through all these collaborations with clinical experts, our simulation goals will stay focused on problems of interest and relevance to the world of health care and will further amplify our impact.

### 2.3 Background and Preliminary Results

#### 2.3.1 Background

Many simulations follow a workflow that is very consistent across domains and we have adopted this workflow as a summary of the simulation pipeline that the Center seeks to implement for a wide range of applications. Figure 2.1 shows this workflow and the various elements that are required to implement it. The final element of the diagram houses the substantial tasks of creating mathematical and then numerical formulations that capture the behavior of interest. Each element, of course, requires some degree of customization to match the specific simulation application, however, a goal of the Center software is, as much as possible, to employ generic tools that can be reused across a range of applications. The others sections of this proposal cover the details of image based modeling, mesh generation, estimation, and visualization so we focus attention here on the specific simulation component.

Figure 2.2 contains a more detailed version of the simulation component of the image based modeling pipeline in Figure 2.1 that outlines the steps required once the geometric model is complete. As with the complete pipeline, there are many variations on the steps in the figure, but the generic form is highly reproduced across many specific examples. The challenges then include 1) the need to formulate suitable mathematical equations to describe the problem of interest, 2) the conversion of these equations into a numerical form suitable for computing, 3) the implementation of efficient algorithms to carry out the computations in feasible time frames, 4) the application of appropriate starting or boundary conditions, and 5) the validation and verification of the resulting simulations.

We now describe the background for some of the specific themes, needs, and challenges of the simulations that make up the goals of the CIBC and its DBPs and collaborators.
2.3.1.1 Multiscale Modeling

A major theme in the Center and simulation of biomedical behavior in general is the need to create models that span scales, *i.e.*, that allow the simulation of behavior across a range somewhere between the genome of an organism and its integrated behavior. Such models allow, for example, the projection of variations or abnormalities that are well characterized at one scale to other scales, often with clinical manifestations as the target scale. Creating useful multiscale models is more complex and more sophisticated than simply developing efficient means to compute large enough numbers of elements at one scale to represent behavior; *e.g.*, simulating the behavior of the heart is not possible by computing the interactions of the billions of cells that make up a heart. Instead, each transition of scale requires a newly formulated biophysical and mathematical approach so that key features at one scale are transmitted to the next in a way that achieves the simplification necessary to enable
computation of results. In the example of the heart, stochastic models of ion channel behavior can be integrated in models based on the classic Hodgkin-Huxley formalism\textsuperscript{19} to simulate whole cell behavior in a way that reflects genetic abnormalities. The transition from cell to tissue occurs by one of a number of simplifying formalisms, most often the biodomain approach,\textsuperscript{20–23} but also cellular automata,\textsuperscript{24–27} reaction-diffusion approaches known as Fitzhugh-Nagumo,\textsuperscript{28–31} monodomain,\textsuperscript{32–34} simplified wave propagation\textsuperscript{7,35} or even hybrid forms of several of these approaches.\textsuperscript{36,37} We describe some of these approaches in more detail, below. Within the Center, we have developed multiscale modeling that makes extensive use of the bidomain formulation and have created a new formulation that we refer to as “microdomain”, in which a model consists of tens to a few hundred individual cardiac myocytes that are organized with highly realistic structure based on myocardial histology\textsuperscript{11,38,39} described in more detailed in Section 2.3.2 below.

A comprehensive term that includes modeling from the genome to the cell is Systems Biology, a field of enormous growth in recent years\textsuperscript{4–6,40–42} attempts to captures this perspective and seeks to combine all elements of the cell to predict overall function through integration of methodologies and functional elements. Simulation plays a substantial in systems biology and numerous relevant software systems are under active development, \textit{e.g.}, ERATO,\textsuperscript{7} E-Cell,\textsuperscript{43} BioSPICE,\textsuperscript{44} and the Virtual Cell\textsuperscript{\textsuperscript{2}} together with a common language developed to describe such models, the Systems Biology Markup Language (SBML),\textsuperscript{7} The NIH/NCBC Center is dedicated in large part to the development of systems biology software to support biomedical research.\textsuperscript{45}

Within the Center, the most frequent building block for simulation of cardiac or neuron electrophysiology is the membrane or cell model based on various forms of the Hodgkin-Huxley formalism.\textsuperscript{1} There exist at least 30 different models of the cardiac myocyte, each for a different cell type or species\textsuperscript{5} and all of which share a fundamental formalisms defined by the discoveries of Hodgkin and Huxley\textsuperscript{1} (for which they received the Nobel prize in 1963. The number of ionic currents in such models has progressed from five (in the Hodgkin-Huxley model) to a dozen or more; recent models have included additional components for intracellular buffering of calcium, regulation of pH, and contraction.\textsuperscript{46–48} We have incorporated into BioPSEa number of specific models of the excitable membrane, in most cases based on cardiac myocytes, and used these as building blocks in tissue and whole heart simulations.

A domain of considerable focus and progress within the Center continues to be the simulation of myocardial tissue. A major motivation for developing such approaches is that electrical instabilities in the heart are the most common cause of cardiovascular death,\textsuperscript{49} a fact that drives DBPs described in this proposal. Mechanical contraction of the heart follows electrical stimulation through a cellular mechanism mediated by ionic calcium currents and release of calcium from intracellular stores.\textsuperscript{50} Given the wealth of information on the cellular components of electrical behavior described above, it is natural for investigators to have coupled individual cells into composite models of tissue. In order to span the step in scale from cell to tissue, investigators have developed a set of surrogate models that capture essential features of cardiac activation and the spread of that activation from cell to cell. The first model capable of simulating the entire heart was based on a cellular automata approach in which regions of the heart corresponding to cubes of 0.5–2 mm, each of which passed through a sequence of discrete states that mimics the action potential of a myocyte.\textsuperscript{25,26,51,52} The major advantage of this approach was its computational efficiency, which led to its widespread use to elucidate mechanisms of atrial fibrillation,\textsuperscript{24} ventricular arrhythmias\textsuperscript{53–55} and body surface maps from focal excitation.\textsuperscript{56–58} The weakness of this approach, however, is its lack of fidelity at fine spatial scales and the need to set \textit{a priori} the effective shape of the action potential.

More relevant for contemporary research are models that make use of the bidomain approach,\textsuperscript{2,20–22,59,60} The essential idea of this approach is to represent myocardial tissue as a continuously varying set of parameters rather than a discrete network of individual cells. The bidomain furthermore assumes that intracellular and extracellular spaces occupy the same physical space and are coupled by an electrically active membrane that generates the active currents the represent the bioelectric source. Because this method includes explicit membrane kinetics, it is more flexible and powerful in its ability to link mechanistically features of cellular and ionic activity to tissue behavior.

An essential parameter for virtually any realistic model of myocardial tissue are the electrical conductivities in the intracellular and extracellular spaces. The conductivities are not scalar values as they depend on the direction of current flow relative to the orientation of the myocardial fibers, orientation that changes continuously in space throughout the heart;\textsuperscript{51} mathematically one represents these as tensor quantities. Because typical tissue models do not contain structural information at the level of individual cells but are in some way schematic or homogenized, the only way to include the effects of structure, cell-to-cell coupling, variations in extracellular space, or changes in electrolyte composition is through the conductivity tensors, or even higher order functional param-
eters such as local propagation velocity. For example, to simulate the effects of ischemia on the myocardium requires alteration of the conductivity values to reflect the increases in extracellular potassium concentration ([K⁺]), movement of liquid from the intracellular to extracellular space and associated changes in extracellular volume, and increases in gap junction resistance. Unfortunately, the relationships between all these parameters at the cellular level and the macroscopic tissue conductivities are not known and follow no simple rules. Thus to achieve truly multiscale simulation requires a means of estimating the tissue conductivities from the cellular structure/characteristics, a step for which we have developed the microdomain formulation, which we describe in more detail in Section 2.3.2, below.

The literature on simulations of mechanical behavior of the heart is much more sparse than for the electrical case, but there is growing interest in predicting normal and abnormal contraction of the heart. The mathematical formulation of heart mechanics is more complex than its electrical counterpart, so that computational costs are much more prohibitive. In addition, the required constitutive properties of cardiac tissue are very difficult to determine from experiments. Despite the hurdles, researchers have developed full mechanical models of the heart and used them to examine passive ventricular characteristics, systolic wall strains during normal contraction and ischemia.

2.3.1.2 Bioelectric source modeling

Bioelectric source modeling is essentially an extension and focusing of the general concepts of multiscale modeling that is specific to a broad class of problems in biomedicine and especially clinical medicine. A bioelectric source is a simplified representation of the electrophysiological origins of endogenous electrical activity in some excitable tissue. The most famous example is probably the current dipole as a representation of the electrical activity of the heart, an idea that is not only the topic of a Nobel prize awarded to Wilhems Einthoven in 1926, but is also the basis of the interpretation of the ECG included in virtually every textbook of physiology and electrocardiography in use today. The same biophysical notion of a current dipole also forms the basis of virtually all commercially available systems for localizing focal electrical activity in the brain.

Although powerful and ubiquitous, the current dipole is not the only useful bioelectric source model in the heart or in the brain. Taccardi et al. showed in the 1960’s that there are features of the body surface potentials on the torso that cannot be explained by a single dipole and in the 1970’s Barr and his colleagues proposed a cardiac source formulation based on the potentials distributed on the epicardial surface. In the 1980’s followed still more formulations, perhaps most important those from Cuppen, Van Oosterom, et al.

2.3.1.3 Numerical approaches

2.3.1.4 Computational approaches

2.3.2 Preliminary Results

2.4 Method

2.5 Impact and Significance

2.6 Facilities
Part III

Section 4: Infrastructure
Part IV

Section 5: Driving Biological Projects
3 University of Utah DBPs
3.1 Real time guidance of atrial ablation

Atrial fibrillation (AF) is an electrophysiological condition that represents an increasing problem in the aging populations of the world; AF significantly increases the risk of stroke and mortality and diminishes quality of life. The best current method to evaluate the progression of AF and monitor the success of interventions is via an invasive intracardiac catheter-based electrical mapping procedure. A non-invasive means to evaluate characteristics of AF prior to treatment and to track the effect of interventions over time would be extremely valuable. Magnetic resonance imaging (MRI) offers such an opportunity. Before MRI can achieve its potential, however, there are very challenging technical problems to overcome, for example the high spatial resolution required to image the thin atrial wall and temporal resolution and gating necessary to compensate for the distorting effects of respiratory and cardiac motion. Based on recent, extremely encouraging progress in overcoming these hurdles, Dr. Marrouche and his team are pursuing a plan for developing and validating in animal models and patients the advances necessary to establish this new form of MRI and greatly improve management and treatment of AF.

Dr. Marrouche’s group, known as the Comprehensive Arrhythmia Research and Management (CARMA) Center, have published recent findings indicating that the MRI methods they have developed may provide a means to evaluate clinically relevant characteristics of the tissue substrate that supports AF. Perhaps even more than with other forms of cardiac arrhythmia, the substrate of the atrial tissue plays a key role in the occurrence of the condition. For example, there is a known but incompletely understood relationship between the extent of fibrotic areas in the left atrium (LA) and the propensity for AF. The DBP investigators have additional compelling evidence of a relationship between extent of fibrosis and subsequent outcome of treatment by means of what are known as ablation techniques. Ablation is a catheter-based treatment that uses some form of energy (typically radio-frequency, RF; but also cooling and laser light) applied to the inner surface of the heart (the endocardium) to electrically isolate the pulmonary veins, which flow into the left atrium and are considered the dominant site of the origin of AF. The basic approach of ablation is the same as the surgical technique known as the Cox-Maze procedure, which seeks through a series of incisions to electrically isolate the atria and thus suppress the coupling that is required for AF. Catheter based ablation is gaining popularity as the least invasive means of curing AF, however, not all patients respond to this treatment strategy for reasons that are not clear but may be associated with pre-existing fibrosis in the LA. Thus the success and hence the choice of treatment may depend on the type and extent of pre-existing fibrosis in AF patients. Dr. Marrouche and his group are investigating the hypothesis that MRI based detection of fibrosis in the left atrium can predict outcome and thus direct patient treatment for atrial fibrillation. A related technical goal is to show that MRI-based approaches are capable of detecting and measuring the extent and spatial distribution of fibrosis in the left atrium and to use the resulting parameters to diagnose and triage patients. The current role of the Center in this project is to provide segmentation software and SCIRun as tools for the evaluation of MRI images in patients with AF. We propose to expand those capabilities based on the interactions with this DBP.

In addition to evaluating patients before treatment, findings by Dr. Marrouche and by others suggest novel utility of MRI in detecting the changes in atrial tissue that result from ablation therapy. Post ablation changes relative to pre-treatment scans reveal the location of successful scar formation and thus allow a noninvasive means of monitoring patient outcomes. Dr. Marrouche and his team, especially Dr. Chris McGann, a cardiologist and imaging specialist, have compared these MRI images to the standard approach known as “electroanatomical mapping”, a catheter based method capable of recording both anatomical location and the associated electrical signal from the heart. Electroanatomical maps track the location of each radio frequency lesion applied to the endocardial surface of the left atrium. Moreover, the progress of the ablation induced MRI changes in subsequent scans (1 day to 6 months) suggests that they could serve as an early predictor of recurrence of AF. These findings lead to a second hypothesis that The progression of MRI based changes following ablation therapy can serve as indicators of recurrence of AF.

The scientific goals of this DBP are to address the hypotheses and technical goals above by developing improved MRI imaging acquisition and processing techniques, by validating their effectiveness in animal models of AF, and then applying the resulting techniques in patients to establish their utility. This interdisciplinary
approach plays on the strengths of three very strong research groups at the University of Utah—in Cardiology, Radiology, and Bioengineering with the Center as the technical partner in developing the necessary image processing and computational capabilities.

The scientific aims of this project are thus:

1. To further develop new MRI acquisition and reconstruction methods with contrast agent enhancement that provide sufficient signal and spatial resolution to characterize the left atrium pre- and post-treatment.

2. To use canine models of induced atrial fibrillation to validate and quantify these methods through functional and histological evaluation before and after ablation.

3. To develop robust post-processing methods for the MRI images and assess the reproducibility of these new acquisition and processing methods in human left atria. We hypothesize that with these methods, pre-treatment fibrosis and post-treatment scar measurements can be obtained with an interstudy variability below 20% and 15%, respectively.

4. To apply the imaging techniques to patients being treated with ablation and determine their ability to predict outcomes based on MRI images of pre-ablation fibrosis and post-ablation scar.

Success in these aims will result in a new standard for non-invasive imaging that will improve the patient-specific selection of treatment of the approximately 4 million Americans suffering from AF and resolve open questions such as how well pulmonary vein (PV) isolation reflects successful ablative treatment. Such a tool would be widely adopted if it could accurately and reproducibly characterize the left atrium before and after the ablation procedure. The proposed studies will also greatly increase our understanding of the process of LA remodeling after treatment of AF with ablation. More generally, these advanced imaging approaches could be extended to non-invasive tracking of LA changes due to a variety of therapeutic approaches aimed at structural or functional improvement.

3.1.2 Background

3.1.2.1 Clinical profile of Atrial Fibrillation

Atrial fibrillation is a growing problem in modern societies with an enormous impact on both short term quality of life and long-term survival. Approximately 0.5% of people aged 50 to 59 have atrial fibrillation and in the population aged 80 to 89, 9% are afflicted with AF—and these prevalences are increasing. While many with the condition go untreated, AF is associated with an almost two-fold increase in the risk of mortality. AF patients experience a dramatically increased rate of stroke, from 1.5% for those aged 50 to 59 years to 23.5% for those aged between 80 and 89, a risk that, by contrast, decreases with age in the normal population. Treatment of AF represents a significant health-care burden with the annual costs estimated at around 7 Billion US dollars.

Restoring and maintaining sinus rhythm remains one of the major goals in treating patients with AF. One treatment modality is a combination of DC cardioversion and initiation of antiarrhythmic drugs, however, only 40–60% of the AF population is maintained in regular rhythm 1 year after such treatment. The treatment itself may also have serious adverse effects and must usually continue for the lifetime of the patient. By contrast, maintaining sinus rhythm without the use of antiarrhythmic drugs seems to be associated with increased survival. The inadequacies of drug-based treatments for AF have long been the major motivation for finding a truly curative approach to maintain sinus rhythm and suppress AF.

3.1.3 Catheter Ablation of AF

The past decades have seen significant progress in understanding some of the underlying mechanisms that promote the occurrence of AF or encourage its persistence and that knowledge has led to a treatment paradigm with great promise but so far unfulfilled potential. The key finding that led to this therapy was the significant role of the pulmonary veins and the left atrium in initiating and maintaining atrial fibrillation. The aim of the resulting therapy has thus become to separate electrically the left atrium from the pulmonary veins. In an effort to increase the penetration of this curative approach, several researchers, including Dr. Marrouche, have instigated various modifications to the ablation procedure aimed at improving outcome and hence promoting the
adoption of the ablation approach by more practicing electrophysiologists. Figure 3.1 shows schematically the contemporary arrangement of catheter based access to the left atrium, under guidance of fluoroscopy and intracardiac ultrasound.

Despite the fact that ablation, when successful, offers a complete and final cure, the success rate of ablation in maintaining regular sinus rhythm without the additional use of antiarrhythmic medications still lies at 40-80%. At least two major obstacles remain that are responsible for the wide variation of outcome related to the AF ablation procedure. The research underway by Dr. Marrouche and his team would target both. The first challenge lies within defining the appropriate candidate for an ablation procedure. The second ongoing challenge is the assessment of the residual extent and effectiveness of left atrial tissue lesions and eventually scars that are the goal of the procedure.

3.1.3.1 Triaging patients to the ablation procedure

Defining an accurate means of identifying AF patients who would likely benefit from ablation would greatly improve the success and utility of the procedure. The basis for such a screening lies in the changes in structure of the atrial tissue that are closely linked to atrial fibrillation. Some of these structural changes occur as a precursor of onset of the disease and some occur as a direct consequence of AF and further entrench the persistence of the condition—hence the expression that “Atrial fibrillation begets atrial fibrillation”.

Currently, predictors such as age, duration of AF, left atrial size, and left ventricular disfunction appear to be associated with a reduced success of the ablation procedure. However, despite this association, only a random subset of patients with these symptoms actually fail to respond to the treatment modality so that such a profile remains a poor predictor of response for individual patients. Other metrics, such as the detection of pre-existing low voltage tissue (or fibrosis), predict procedural success with higher fidelity; however, pre-existing voltage levels in the heart can only be determined through invasive electrophysiology study of the atrium. Determining the level of fibrosis usually requires histological studies. Exciting preliminary data from Dr. Marrouche’s group has shown that it may be possible to assess non-invasively by the use of DE-MRI the location and extent of structural fibrosis within the left atrium prior to ablative treatment.
3.1.3.2 Assessing left atrial tissue damage caused by the ablation procedure

A second major challenge associated with AF ablation is the assessment of left atrial tissue damage and especially its persistence and changes over time. As many as 30–40\% of ablation cases return with recurring AF and the likely cause is functional (electrophysiological) recovery of the initially ablated tissue. Developing imaging techniques that would allow characterization of the lesions from ablation and quantification of the properties of the LA before and after ablation could have a huge impact on the success of the procedure. Such achievements would not only improve existing ablation approaches, but also provide a key tool for performing the procedures under real-time MRI guidance. Achieving the ability to measure lesion formation in real time or even near real time (within minutes) would improve accuracy of lesion placement and reduce the unwanted recovery of ablated tissue, and subsequently reduce the risk of perforation and fistula by visualizing the depth of the delivered lesion. Achieving these goals would improve success, reduce the need for repeated treatments, and minimize the risk of major complications associated with this procedure.

A novel aspect of Dr. Marrouche's research is the attention to the process of RF ablation and its consequences on tissue properties over the course of the peri- and post-procedural period. RF ablation is performed with energy in the frequency range of 500 kHz applied for tens of seconds from an electrode that is integrated into a venous or arterial catheter. The RF current flows from the tip of the catheter through the patient to the grounding pad, causing high energy densities in the region adjacent to the catheter (approximately 1 mm, depending on power levels and catheter size) and thus rapid heating of the tissue and blood. The response of the tissue to the RF energy includes coagulation necrosis in the immediate area and a reduction in blood flow, which arises from microvascular endothelial injury.

Relatively little is known about the response of the tissue in the period following application of the RF energy. Lesion size appears to remain roughly the same over 3 weeks post-ablation, though the sample size of this study was small (5 dogs). What follows ablation is likely a period of edema, cell death, and denaturing of proteins leading to scar formation. At a macroscopic scale, reverse remodeling also occurs, leading to shrinking LA volume at 3 months, a finding that is known to indicate successful RF ablation. Conversely, additional LA dilation is found post-ablation in patients who do not maintain sinus rhythm. Less well understood, and one focus of this study, are changes of time of lesion size and the amount of long term scar and fibrosis in the left atrium.

3.1.3.3 MRI guided ablation of atrial fibrillation

A third application of MRI to the treatment of AF is to integrate the imaging into the ablation procedure itself. The concept of MRI guided interventions is quite novel but has already gained recognition in a range of applications such as peripheral vascular disease, and a range of other applications in musculoskeletal system. Although applications in cardiac interventions are made more challenging because of the heart motion, there has been notable progress in recent years in developing this application domain through animal studies.

The advantages of MRI guidance over the current standard of a combination of CT, floroscopy, ultrasound, and electroanatomical mapping include the illumination of radiation load on patient and clinical staff, enhanced visualization of soft tissue, and the potential to integrate imaging modalities and thus greatly simplify the persistent challenge of image fusion, registration, and visualization. Perhaps most attractive is the potential for instant visualization of lesion formation and thus the opportunity to evaluate the anticipated success of each lesion based on its degree and extent—in principle, it is possible to use MRI to visualize lesions in the heart walls as they form. Such a system would dramatically reduce the rate of reoccurrence of the arrhythmia and also mitigate or even eliminate the risk of perforation of the heart walls or the creation of ulcerous fistula between the left atrial chamber and the esophagus. This latter complication is the most severe and most feared in clinical ablation practice. MRI also allows tracking of devices within the body by means of coils that are tuned to the MRI scanner, providing a means to record and to display catheter position in the same display as the heart tissue.

There are many many challenges the impede the easy application of MRI to cardiac interventions in the atria. Most obvious are the extremely high resolutions required to identify structures of interest, which are often only a few millimeters in size. High spatial resolution always comes at a cost in imaging time and the result for imaging of the heart is reduced temporal resolution. With the heart beating—during AF at a very rapid rate with little beat to beat consistency—the choice of pulse sequences is a clear trade off between spatial and temporal resolution and spatial coverage. ECG gating can restore the spatial resolution but at a cost of many heart beats to carry
out volumetric imaging. A further source of spatial error is the movement of the heart through respiration, which can result in centimeters of error between the assumed and actual location of a catheter with respect to the heart. With the entire left atrium only a few centimeters in cross sectional dimensions, spatial uncertainty must be kept in the range of a few millimeters in order to carry out the ablation procedure safely and effectively.

A goal of the Center in the context of this DBP will be to implement registration schemes that will seek to correct for systematic spatial errors arising from cardiac and respiratory motion. We will also develop visualization paradigms that will support the merging of information from imaging, catheter location and path, and electric potentials acquired during ablation procedures in a way that enhances the clinicians ability to consume and utilize this diverse information.

3.1.4 Imaging of the Left Atrium: Identification of fibrosis, scar, and edema in the heart with MRI

Imaging of the left atrium with a variety of modalities including ultrasound, X-ray fluoroscopy, CT, and MRI is critical in the current assessment and treatment of atrial fibrillation. Many studies performed on the anatomical structure and function of the left atrium have utilized a wide array of imaging modalities. For example, Tsao et al.\textsuperscript{115} used MRI to study structural remodeling of the PV and LA after catheter ablation. From these studies, the atria and PVs tend to return to more normal sizes and shapes within 12 months, however, in some patients with late recurrence of AF, the LA tended to increase in size. Ultrasound is not as precise as MRI or CT for quantifying morphology, and new MRI and CT techniques will shed light on the relationship between the function and the changes in anatomy and composition of the LA that occur over time in response to AF and to ablation treatment. More recently, MRI methods have emerged that go beyond anatomical measurements to identify tissue characteristics and we describe some examples below.

**Imaging with gadolinium contrast agent** Studies of myocardial tissue viability using gadolinium and MRI are now well established for assessing acute and chronic scar in the left ventricle. Delayed imaging at diastole on the order of 20 minutes after injection of \( \approx 0.2 \text{ mmol/kg} \) gadolinium with an inversion recovery sequence gives enhanced signal in scar regions. The enhancement is thought to be due to the larger distribution volume in regions with dead cells\textsuperscript{116} and this form of imaging of scar with MRI (delayed enhancement or DE-MRI) is now considered the gold standard for non-invasive measurements in the LV. Landmark studies by Lardo et al.\textsuperscript{117} showed that it is possible to image recent large ablations in the apex of the right ventricle of dogs, with or without injection of gadolinium contrast. Dickfeld et al. recently reported delayed enhancement in RF ablated areas on the epicardium of the right ventricle in open chest animal studies.\textsuperscript{119}

Peters et al.\textsuperscript{76} and more recently Dr. Marrouche and Dr. McGann’s group\textsuperscript{119} as well as others\textsuperscript{120} have developed a high resolution three-dimensional MRI method that makes it possible to perform delayed enhancement imaging of the very thin LA wall in some patients. Using this approach, comparisons between pre-ablation and post-ablation images reveal increased enhancement, likely due to scar caused by ablation. There is also evidence of a more diffuse enhancement in some patients prior to ablative treatment, which Dr. Marrouche and has groups have described in a recent landmark study in the leading journal in cardiovascular medicine.\textsuperscript{121} Pre-ablation enhancement is more subtle than post-ablation and is spatially associated with regions of low amplitude voltage on the LA endocardium, as is described in.\textsuperscript{121} The Marrouche group will attempt to answer the outstanding question regarding the relationship between DE-MRI findings and tissue features from histology based on animal models of AF.

A persistent challenge in this and most novel applications of MRI is to establish acceptable repeatability of the measurements. There is some data on DE-MRI in the LV, but none yet in the LA that shows consistent measurement of the size and location of delayed enhancement in the left ventricle (\( \approx 8.6\% \) interstudy variability, also termed coefficient of variation, CV).\textsuperscript{122} For long term (8 months) reproducibility, Bulow et al.\textsuperscript{123} found that the size of late enhancement regions did not differ significantly, regardless of whether or not an intervention was performed.\textsuperscript{123} Interstudy variability of infarct size was \( \approx 11\% \) (estimated from Fig. 4 in Bulow et al.\textsuperscript{123}). However, others have reported in 40\% of patients undergoing bypass grafting, an increase in the size of the infarct region of typically 5\% of the LV mass.\textsuperscript{124,125} In the LV, infarcts have been shown to shrink on the order of four-fold over 8 weeks in patients\textsuperscript{126} and in canines.\textsuperscript{127} Recent studies by Schmidt et al. quantified non-uniformity within the DE-MRI images of the LV, and correlated such heterogeneity with increased risk of reentrant arrhythmias. They reported that the size of the “gray” zone, which is the more heterogeneous portion of the DE-MRI images
(normal and core infarct regions were more uniform), was the only marker that matched significantly with the inducibility of ventricular tachycardia in 47 patients.\textsuperscript{126}

These results imply that DE-MRI is a useful tool for assessing the interplay between the size and composition of fibrosis and the likelihood of atrial fibrillation.

**Imaging without gadolinium contrast agent** There is mounting evidence to suggest that MRI without contrast agent can also visualize ablation lesions. The same study by Lardo \textit{et al.} describing DE-MRI to image ablative damage also reported that contrast agent was not essential to capture large ablations in the apex of the RV in dogs.\textsuperscript{117} T2-weighted fast spin echo images were acquired in two 2D slices every 2 minutes post-ablation for 20 minutes. Approximately 30 minutes later, T1-weighted images were acquired just before and after injection of gadolinium contrast. The lesions could be seen in both the T2 and T1-weighted images. The lesion size corresponded approximately to size from histology. Dickfeld \textit{et al.} recently extended this approach to acquire T2 and T1-weighted images taken from 30 minutes to 12 hours after ablation with and without the use of contrast agent.\textsuperscript{129} Ablations were performed in open-chest canines on the epicardium of the RV and lesion size estimates were unchanged over the 12 hour acute time period, although contrast and signal decreased over time.

Acquiring parametric maps of T1 with a spoiled gradient echo sequence could have several advantages over the conventional DE-MRI approach. Conventionally, an inversion recovery (IR) sequence is used, with a readout of the k-space data at time $T_I$ (time after inversion). A TI is chosen to null the regions of normal LA wall and/or blood in order to improve the contrast with scar, which will have a shorter T1. One problem with this approach is that the IR sequence is not arrhythmia-independent. If heartbeats are of different length, there is a disruption of any steady-state already achieved since not all of the protons will have recovered after the IR pulse by the next heartbeat. Imaging every other heartbeat could reduce this effect but would double the scan time. Such delays could be especially important in patients with high heart rates.

**3.1.4.1 Methods for sizing of enhanced areas in DE-MRI Studies**

Most viability studies of the left ventricle have been interpreted visually and not quantified; a major goal of the research by Dr. Marrouche's group and this DBP is to develop image processing approaches that permit quantification. In the ventricle, wall thickness of the hyperenhanced area correlates well with functional recovery or lack thereof in post-revascularization studies so that quantification is also an attractive goal. Quantification of the size of the non-viable area has been performed with thresholds relative to a normal region (2–3 standard deviations (SD) above normal) and has been validated in animal models.\textsuperscript{127} Through a collaboration with the CIBC, Dr. Marrouche and his group have developed similar approaches for sizing enhanced areas in the LA, though they typically require manual input.\textsuperscript{130,131} At least two semi-automated methods for quantification in the ventricles that operate within traced myocardial contours have appeared in the literature. One used fuzzy c-means clustering to classify normal and non-viable pixels.\textsuperscript{132} The other used a level sets method and a statistically derived threshold and came close to performing as well as manual delineation by experts.\textsuperscript{133} Implementing these and other approaches will be one of the projects that will be part of this DBP.

**3.1.5 Animal models of atrial fibrillation**

While imaging of ablation lesions in ventricles has shown some success, to date, there are no published reports of MRI imaging of lesions created in the LA of an animal model over acute or chronic time intervals. Nor have animal models of AF been employed in such studies. This is a critical gap in knowledge that the research of Dr. Marrouche and his team will seek to fill. The emphasis in most published studies has been on real-time MRI for guidance and lesion characterization during ablation procedures. The CARMA team will focus instead on the development and use of MRI techniques to increase understanding of the structural changes and their functional electrophysiological consequences and to improve the management of AF by appropriate selection of ablation procedures.

The use of animal experiments to study atrial fibrillation covers over 100 years and such studies remain the dominant source of information regarding mechanisms of the disease.\textsuperscript{134,135} The source of most recent knowledge are the numerous forms of induced atrial fibrillation that vary both in their choice of species and the means of creating fibrillation, with the majority involving some form of chronic rapid pacing of the heart.\textsuperscript{97,134–136}
While each of these models has been shown effective at inducing AF, none induce all of the substrate changes observable in clinical AF. Because no animal model of AF matches all clinical criteria, it is necessary to base the selection of an experimental model system on the specific facet of AF to be studied. Of special importance is the ability of such models to create remodeling of the heart so that AF continues even after termination of the rapid pacing. Moreover, there is growing consensus that remodeling includes both electrical or ionic current remodeling and structural remodeling, and that different protocols will create different combinations of these two facets of the disease.

The rapid atrial pacing (RAP) model is based on the concept that “atrial fibrillation begets atrial fibrillation.” Conditions for AF are induced by rapidly stimulating (pacing) atrial tissue (≈ 600 beats/min), with an implanted pacemaker, as though it were already in atrial fibrillation. The result is a heterogeneous decrease in atrial effective refractory periods (ERPs) and tissue refractoriness, which substantially increases susceptibility to multiple circuit reentry. These changes to the atrial substrate constitute electrical remodeling but neither the size of the left atria nor the level of interstitial fibrosis (structural remodeling) are significantly impacted by the RAP model.

Mitrval valve regurgitation (MVR) is a condition often associated with AF and induced MVR increases vulnerability to AF. The MVR animal model is initiated by catheter avulsion of the mitral chordae and this model is effective at inducing changes in atrial substrate that increase vulnerability to AF. Substrate changes in MVR include increased interstitial fibrosis, and left atrial dilation, which represent structural remodeling. Moreover, AF induced by burst pacing can be maintained for extended periods. However, one limitation of the MVR model is the irreversibility of the mitral chordae avulsion, which prevents the study of AF independent of symptoms specific to the regurgitation.

Congestive heart failure (CHF) is strongly associated with AF and when experimentally induced causes an increased vulnerability to AF. In animal models, CHF can be induced by rapid ventricular pacing (≈ 240 beats/min) over a period of weeks. Similar to the MVR model, CHF induces structural changes in the atria including dilation, fibrosis, and high vulnerability to AF. In addition, electrical remodeling by CHF is not significant. However, unlike the MVR model, termination of the ventricular pacing spurs recovery from the general effects of CHF. In addition, following recovery from CHF symptoms, interstitial fibrosis and the ability to induce AF are conserved.

A recent variant or hybrid of these approaches includes pacing of both chambers, which has shown promising results after fairly short (2 week) duration. In this model, both the atria and ventricles are paced simultaneously, thus minimizing the normal delay between atrial and ventricular contraction that allows the atria to pump through the open atriioventricular valves. Instead, the atria pump into closed valves and thus experience increases in atrial pressure that lead to dilation, fibrosis, and susceptibility to AF. A substantial advantage of this approach is that it produces less ventricular damage and more atrial remodeling so that the survival rate is enhanced, there is greater consistency across animals, and the resulting state may be more representative of human AF, especially paroxysmal forms. Of special importance for the proposed studies is the evidence that combined atrial and ventricular pacing has shown to produce higher levels of collagen, and thus fibrosis, than either atrial or ventricular pacing alone. This type of AF model therefore opens up new opportunities for the study of the full spectrum of the disease and applying imaging techniques to quantify both pre-treatment fibrosis and post ablation lesion and scar.

### Investigator profile

The leader of the AF ablation group is Nassir F. Marrouche, M.D., who is well suited for this program and uniquely trained and able to lead this interdisciplinary team. He joined the University of Utah in September 2006 after extensive training at world renowned institutions. He studied medicine and cardiology in Germany at the Universities of Heidelberg and Würzburg, respectively, and then completed training in electrophysiology at UCSF and Cleveland Clinic in the US. During that time, he initiated medical and technical projects with the aim of improving the success and effectiveness of ablation in the treatment of AF, documented by peer review publications and presentation on all aspects of AF and its management. In the course of over 1000 electrophysiology procedures performed, he has also developed new catheter modalities for mapping AF. He has greatly expanded the use of real time intracardiac echocardiography (ICE) as an imaging modality to guide the placement of catheters in the left atrium. Even in his short career, he has consistently been a successful leader in the development of innovative ideas for integrating advanced imaging and device technologies to expand the capabilities of his discipline. He continues to challenge the existing paradigms of clinical electrophysiology by...
seeking to bring diverse technologies such as ultrasound, MRI, advanced image processing and analysis into new arenas.

In the three years since coming to Utah, Dr. Marrouche has quickly established a clinical practice and gathered a collaborative interdisciplinary research team consisting of internationally known scientists and engineers who share his dream of improved AF detection and management. This group, known as Comprehensive Arrhythmia Research and Management (CARMA) Center consists of over 30 members who are physicians, engineers, physicists, and fellows, students, and staff from all over the University of Utah campus. He has also received the support of the University of Utah to create a completely unique integrated MRI/Catherization suite, which contains both a state of the art clinical cardiac electrophysiology facility combined with a dedicated 3 Tesla MRI system. Patients can move along tracks between the fluoroscopy based electrophysiology room to the MRI scanner and back again so that MRI can be fully integrated into patient treatment and care. This suite is also available to the CARMA team for animal research and for developing and testing novel techniques for imaging, image processing, and mapping of cardiac bioelectricity. Leading industrial partners such as Siemens, Biosense Webster (of Johnson and Johnson), and Surgivision Inc. have committed their resources and support to his vision.

3.1.6 Significance of the proposed collaboration

Success in this research would re-define the way physicians approach treatment and management of atrial fibrillation. This proposed research targets important challenges that would modify all phases of management of the AF patient. Definition of pre-treatment left atrial tissue enhancement would have implication beyond the scope of ablation therapies. In addition to being able to define responders to the ablation procedure by assessing the severity of pre-existing conditions, successful evaluation of MRI images would extend this method to other treatment modalities of AF. Patients undergoing medical treatment, pacemaker implantation, or initiation of long-term anticoagulation to avoid stroke would be managed based on the degree of atrial fibrosis and hence receive adjusted/individualized attention and options. Moreover, by standardizing cutoffs of AF progression within the atrial tissue, we would be able to establish a new Atrial Fibrillation classification system similar to the highly useful NYHA classification of heart failure.

Another breakthrough associated with this research is the identification and quantification of left atrial tissue injury caused by ablation. Every practicing physician performing any kind of ablation procedure is starving for feedback regarding the amount of damage caused by his/her ablating within a specific atrial or ventricular site. Results from this collaboration will be able to offer the operator a complete and precise insight into degree of injury, its interaction with the disease, and its correlation with collateral organ systems. Visualization of the left atrial wall and pre- and post-ablation lesions is crucial for increasing our understanding and improving treatments for the growing population of patients with AF.

The MRI developments here could also form the basis towards the goal of observing ablation lesions as they form, or “as-it-happens”. The introduction of real-time MR into the EP lab that would alleviate a significant amount of the hurdles currently facing physicians performing ablation procedures.

This DBP represents an ideal test bed for research and development proposed for the Center TRDs, especially in the areas of image based modeling, visualization, and simulation. The entire basis for pre-ablation evaluation of fibrosis is based on segmentation and quantification of subtle features of delayed enhancement MRI, a process that will require innovative image processing and analysis to achieve. The CARMA team already makes daily use of Seg3D and drives many of the features that it contains. There is a pressing need for still more capabilities so that steps that still require considerable manual evaluation and specific medical experience can become at least semi-automated. Improvements in Seg3D has reduced processing time for a single clinical case from several hours to several tens of minutes but for routine use in clinics, this processing has to be completed while the patient is still in the scanner. Although Seg3D has streamlined the processing by reducing many steps that involved a plethora of software, there are still steps that require hand coded MATLAB programs and other third party programs, each requiring a file conversion and introducing delays and increased chances of error.

Visualization of the multimodality data that arises in AF ablation is also a challenge for which the Center is very well suited. The visualization capabilities of SCIRun are extremely flexible and this tool is used also daily by members of the CARMA group to analyze and visualize results from both patient and animal studies. Specialized tools like map3d and ImageVis3D are also part of the tool kit that is required for both the clinical and research aspects of this project. Real time, MRI guided ablation will be an exciting opportunity to define
new paradigms for visualization as pre-acquired MR angiography, segmented volumes, real time MRI slices, recorded and real time catheter positions and trajectories, and bioelectric potential data all need to be merged, registered, and flexibly displayed for the interventionalist. The visualization of geometrical uncertainty would also add greatly to the information conveyed at all stages of the patient management and especially in situations like real time MRI guidance in which the impacts of errors must be available to the physician in order to guide the ablation procedure. The Center has experience with multimodal, multiscale, and quantitative visualization of large sized data sets and is well positioned to develop the tools that will help change the way AF is managed.

In order to account for registration and heart motion errors in this DBP, we anticipate the need to develop new simulation models that capture these motions and are driven by spatially and temporally sparse real time information. In this way, high resolution, ECG gated scans of the heart before the ablation (either MRI or CT) can merge with real-time updates in a way that maintains accurate spatial context and precise guidance for the physician. Thus the simulation TRD will also have a valuable role that will include developing such models and then implementing them in a form that permits rapid updates and real time performance in a very demanding setting.

The physicians, biomedical engineers and physicists of the CARMA group are generally not trained in image processing, visualization, and efficient simulation and there are no integrated software tools available for this completely novel application of imaging. The Center has played a key role in the progress to date and will continue to be essential partners in this project.

The techniques required for image processing of DE-MRI and for real time MRI guidance of medical interventions also have broader application that just AF. DE-MRI is useful for all manner of cardiac pathologies as well as other organs that undergo soft tissue changes in the face of pathology. MRI guided interventions are already emerging in all many of clinical specialties and many of the same needs for image processing, quantitative analysis, registration, and visualization arise in those specialties. For example, respiratory motion is a factor in any region of the thorax. Merging of image data is required for all many of MRI and CT based evaluations of vascular disease, cancer, or musculoskeletal disorders, whether for serial studies of single patients or cross sectional analyses of multiple subjects.

3.1.7 Rationale for the proposed approach to the problem

The overarching technical goal of this DBP is to support with a range of computational tools the screening, management, treatment, and maintenance of people with atrial fibrillation. These tools will be useful for all stages of the disease and its treatment, will be simple and efficient to use, and will integrate all the tasks required for patient specific management into a single workflow. The specific technical aims of the DBP include the following:

Registration and segmentation of images from AF patients: We will develop and implement existing algorithms for the broad range of registration and segmentation needs of the AF project.

Quantitative analysis of pre-ablation fibrosis and post ablation edema and scar: We will develop patient and scan specific normalization approaches that allow for robust identification and quantification of enhanced myocardium in MRI images corresponding to substrate changes that effect the occurrence of arrhythmia.

Compensation approaches for errors in position from heart and respiratory motion: We will develop patient-specific simulation models of cardiac and respiratory motion that will allow for correcting errors in reporting position of images relative to each other and of devices introduced into the heart.

Integrated visualization for real time, MRI guided AF ablation:

3.1.8 Methods and procedures

3.1.9 Impact of the Center resources and technology on the project
3.2 Simulation of electric stimulation for bone growth

(1) Collaborating Investigator(s): Roy Bloebaum, Brad Isaacson
(2) Institution: University of Utah (3) Current project funding status: Department of Veterans Affairs Rehabilitation Research Fellowship, University of Utah Technology Commercialization Grant.

3.2.1 Introduction and scientific goals of the collaboration

Osseointegration is a surgical procedure that provides direct skeletal attachment between an implant and host tissue with proven success in dental, auricle and transfemoral implants [1-4]. However, one challenge with using natural biological fixation is attaining a strong skeletal interlock at the implant interface, a prerequisite for long-term implant function [5]. To prevent osseointegration failure at the bone-implant construct with a two stage procedure, extensive periods of restricted load bearing are required to allow for sufficient bone remodeling [6, 7] and prevent overloading [8, 9]. However, loosening at the bone-implant interface from osteopenia [10], stress shielding [11-13] and a lack of loading is a potential concern which must be addressed.

Veterans with combat related injuries form an especially relevant population that require the development of new tools to enhance the success of osseointegration, due to their limited residual limb length caused by explosive devices. Improvements in medical care and evacuation strategies have led to an increase in survival rates, resulting in an elevated number of veterans with amputations that require follow-up care and extensive rehabilitation. The relative youth and otherwise good health of these amputees make them an ideal population for aggressive rehabilitation but also reveal the limitations of current technologies of prosthetic attachment [6]. Current European rehabilitation programs for transfemoral amputees with osseointegrated implants require slow progressive weight bearing determined subjectively by clinicians [14, 15]. While this method is advocated for two stage surgical procedures, “the development of new surfaces and clinical techniques has enabled a marked reduction of the initial healing period, even to the point of an immediate/early loading of implants that show high primary stability” [4, 14]. In addition, physical limitations with warrior amputees using sockets include heat/sweating in the prosthetic socket [6], skin irritation [16] and inability to walk on challenging terrain [6]. To further complicate rehabilitation efforts, a significant number of returning service men and women have short residual limbs for which socket technology is not suitable.

Utilizing metallic implants as a means of biological fixation has been the objective of orthopedic surgeons over the past two centuries [17]. However, controlling osteogenesis at the implant interface, which is essential for providing strong skeletal fixation, remains challenging. Regulated electrical stimulation has proven effective in fracture healing and non-traumatized bone models [18, 19], but has not been investigated in a percutaneous osseointegrated implant system. One advantage of this patient population is that an orthopedic implant protrudes from the residual limb functioning as an exoprosthesis attachment and may operate as a potential cathode for an external electrical stimulation device.

Therefore, the objective of the proposal is to build upon the previous, well proven, clinical success of electrically induced bone growth used to augment fracture healing and expand this technology to accelerate osseointegration in the percutaneous model for veteran and warrior amputees. Since osseointegration technology is still fairly new for lower extremity amputees and not utilized clinically in the United States, ways to increase its efficiency are still developing. The investigator is addressing this limitation by developing an Osseointegrated Intelligent Implant Design (OIID) system which has been awarded a United States provisional patent with the University of Utah Technology Commercialization Office as a novel rehabilitation tool to improve osseointegration technology. The addition of electrical stimulation may increase the rate, magnitude and quality of initial skeletal attachment to the osseointegrated prosthetic stem.

3.2.1.1 Research Question / Hypotheses:

To validate the general hypothesis that electrical stimulation will increase skeletal attachment, a two phase project has been designed that utilizes in vitro, in vivo, and in silico modalities to confirm the safety and efficacy of this technology prior to implementation in veteran and warrior amputees. The specific hypotheses for this model are founded based on histological assessment, mechanical testing, and finite element analysis and include:
In vitro Hypothesis (Collaborative study with WRAMC)

Specific Aim 1: Finite element based simulation analysis of veteran and warrior amputee residual limbs imaged with computed tomography scans will reveal that safe and effective current densities and electric fields will be attainable at the bone-implant interface.

In vivo Hypotheses (Preliminary funding provided by the University of Utah Technology Commercialization Office)

Specific Aim 2: Electrical stimulation will increase the mineral apposition rate of cortical bone at the periprosthetic interface when compared to control implants.

Specific Aim 3: Enhanced bone remodeling, signified by differences in gray levels analysis from scanning electron microscopy (SEM) will demonstrate expedited remodeling near the electrical implants compared to contralateral controls.

Specific Aim 4: Higher forces will be required to remove implants in the medullary canal when subjected to controlled physiologic mechanical push out tests of the electrical implants.

3.2.2 Background of the collaboration

Electrical stimulation drastically altered the field of medicine shortly after Galvani discovered that an accidental electrostatic shock resulted in muscle fiber contraction of an immobilized animal [20]. While the exact reason for this phenomenon was largely unknown at the time, advancements in modern science have demonstrated that endogenous electrical signaling affects tissue growth, repair and regeneration [21-23]. In general, all animals are complex electrodynamic systems with large but stable gradients that direct cell migration [24, 25]. Messages are transmitted from adjacent cells and the neighboring environment by a plethora of available mechanisms including mechanical deformation which affects electrical polarization within a cell membrane [26].

Early research by Brighton and Friedenberg [18, 19, 27, 30, 39] used the concept of electrical stimulation for bone regeneration in the 1960s and 1970s and demonstrated that direct current (DC) could be used to repair non-unions in a shorter period of time when compared to traditional healing methods. Additional models have investigated bone formation with restrictive weight bearing causing induced osteopenia and using low-frequency electrical fields stimulating osteogenesis with a thirty-one percent increase in osteogenic activity between controls and electrically stimulated limbs [37].

While researchers in the field of electrical stimulation have paved the way for understanding the mechanism for osteoblast matrix deposition with electrical stimulation, inadequate understanding has limited the expansion of this technology. While there are many cases of successful healing of non-unions and fracture healing models, examples of patient discomfort and failed attempts are replete in the literature as well [22, 40]. The problem with electrical stimulation occurs from scientists and clinicians controlling the wrong electric metrics and concentrating solely on current magnitudes. Previous researchers have looked to current as the “magic bullet” to fixing the approximate 500,000 non-unions which occur annually [41]. However, repeatability between models has been limited from joule heating complications [42] and not determining current densities [43]. In fact, all manufactured biomedical devices must be limited to a current density less than 2 mA/cm² as outlined by the International Electrotechnical Commission to prevent localized tissue necrosis and patient discomfort [44].

The advantage of using veteran amputees with osseointegrated implants is that a percutaneous post serves as an ambulatory aid and may be developed as an exposed cathode for electrical stimulation. The presence of an osseointegrated implant does not require additional surgical procedures to insert electrical components, allows the device to be controlled externally and prevents further risk of infection [45]. Therefore, by understanding the method of current injection into the residual limb of veteran and warrior amputees an electric field on the magnitude of 1–10 V/cm may be established, controlled and measured at the implant interface. It is hypothesized that this will allow safe levels of electricity to be delivered, capable of inducing osteoblast migration and improving skeletal attachment [36]. An electric field of this degree will increase the quantity and quality of bone at the implant interface, and improve the prospects for accelerated rehabilitation and skeletal fixation for an amputee. Use of electrical stimulation has not been investigated as a modality to accelerate osseointegration in an intramedullary prosthetic implant and presents numerous opportunities for translational research to improve patient care.
3.2.2.1 Investigator profile

Roy Bloebaum, Ph.D. is Research Professor and Albert and Margaret Hofmann Chair in Orthopedic Research at the University of Utah. He is internationally recognized as an expert in bone healing and total joint replacements and holds positions as a research professor in Orthopedics, Bioengineering, and Biology. Dr. Bloebaum is a Research Career Scientist and Co-Director of the VA Bone and Joint Research Lab, which is a collaborative research program with the VA Salt Lake City Health Care System Research and Development Program and is mainly supported by the VA, Health Administration Research and Development Merit Review Program. Dr. Bloebaum’s publications include over 115 peer reviewed manuscripts on bone and total joint replacement related topics and he has been a guest lecturer on these topics all over the world. Dr. Bloebaum’s current research focus is developing alternative prosthesis attachments for warrior amputees and this concept is funded in part by the DOD, TATRC, NIH and PRMRR.

Since the research proposed has the potential to influence rehabilitation clinicians, orthopedic surgeons and scientist alike, the investigator has established collaborative support with Dr. Joseph Webster M.D., (head of Rehabilitation for amputee care at the SLC VA), Dr. Peter Beck M.D., (orthopedic surgeon and voluntary staff physician for the SLC VA) and Dr. Larry Meyer, M.D., Ph.D. (Associate Chief of Staff for the SLC VA).

3.2.3 Significance of the proposed collaboration

This DBP is extremely well aligned with the goals of the Center and will drive substantial progress in all of the TRDs. Thematically, the project builds on the established strengths of the Center in bioelectric fields but expands the application of that knowledge into completely novel and highly significant directions. There are close parallels between this DBP and that of Dr. Triedman directed at simulating defibrillation in the heart. Both DBPs require the creation of highly detailed, patient specific geometric models from image data and then seek to use these models to simulate the effects of artificially applied electric fields on biological tissues. Both DBPs require extensive support for image based modeling, for visualization of image data, and for sophisticated visualization of the simulation boundary conditions and their results. Both DBPs also share enormous potential for the creation of novel estimation approaches with which to predict ideal parameters for applying the external electric fields. In this DBP, the relevant parameters include the placement of the surface electrodes that form the anode for the application of stimulation and the value of the applied field. To further reinforce the similarity between this and the Triedman DBP, preliminary results included below were generated with Seg3D and SCIRun using many of the same specific tools and settings as with the defibrillation project.

While progress on this DBP has been substantial already, there are many additional hurdles that the Center will need to address in the future, challenges that represent ideal test beds for all the TRDs. Specific examples of these challenges include the following:

**Image based modeling:** A major step in the work flow of this project is the creation of accurate and detailed geometric models from CT imaging of actual patients and of animals used for validation. ??Ross: can you add some relevant specifics??.

**Visualization:** Visualization for this DBP includes both the viewing and quality control of the raw image data and the visualization of simulation results. Of special importance to this project is the need to capture uncertainty in the parameters of the model and visualize the consequences of this uncertainty in terms of relevant electric stimulation parameters. Investigators will need to determine the range of useful positions of the surface electrodes and the consequences of variations in those positions. The research will benefit greatly from visualizations of the impact of variations of the applied field strength and the impact of variations in electrode contact impedance. They will wish to see these impacts displayed in terms of variations in electric potentials, spatial current densities, and the associated rates of bone growth. Thus there will be a need for highly integrated display of scalar, vector, and even tensor quantities that may be time dependent and have associated uncertainties.

**Simulation:** Simulation is at the very core of this project and virtually all proposed improvements in simulation infrastructure will assist with this DBP. Computation time is a significant limitation in problems like this in which many iterations will be required to determine optimized settings for relevant parameters. Thus, any progress on computational efficiency will have enormous impact. The problem is inherently multiscale in that it includes macrosopic application of electric fields through electrodes that are embedded in the
bone and applied to the surface. The actual effect of the field, however, is entirely microscopic so that comprehensive simulation approaches must include both levels of interaction to provide comprehensive guidance for implementing this approach in patients. Validation and verification are essential elements of projects like this and the Center will support the use of simulation tools to animal experiments that will both test and confirm the accuracy of simulation and certainly drive new needs in the numerical solutions and computational implementation of those simulations.

**Estimation:** This DBP offers an ideal example of the need for estimation and optimization that are specific to the problem at hand and to the specific subject to which the therapy will be applied. Estimation can go beyond testing “What if?” and begin to answer the question “How is best?”. Implementing appropriate schemes to carry out this estimation process will be challenging because there are few standard approaches that are guaranteed to provide the desired results. However, as with the defibrillation DBP, we will develop and apply both existing and novel approaches and measure their effectiveness based on parallel biological and experimental studies using both *in silico* and *in vivo* models.

It is safe to say that the Center will play an essential role in the simulation component of this DBP and that without a full suite of appropriate software that is well matched to the specific application domain, progress by the investigators would be severely limited. There do not exist standard tools for many aspects of this problem and especially not for the proposed estimation approaches. It is also evident that simulation is highly integrated into the research proposed by the DBP team and has already played a role in showing viability of the entire concept (see below). We note also that simulation of bone growth by electric fields has been reported in the literature for many decades but that its impact has remained limited, in part, because of an absence of planning tools with which to create workable electrode configurations. The fact that the bone implant itself provides one of the electrodes for this application and that simulation provides a patient specific means of evaluating and selecting the location of the second electrode(s) makes this a breakthrough application that simply requires simulation for guidance and optimization.

### 3.2.4 Rationale for the proposed approach to the problem

The basic computational approach in this DBP has been established through ongoing studies and documented in publications (see below) so that there can be little doubt about the basic rationale for our approach. We have been able to show that it is possible to start with CT image data from amputee patients and create patient specific models for those patients that form the basis of simulations of applied electric field for osseointegration.\(^{144,145}\)

Together with the investigators of the project, we have demonstrated the need for customized models over schematic versions created by artificially truncating full-limb models, a need that will be even greater in the planned studies of what is known as *heterotopic ossification* (HO), an overgrowth of mature osseous bone in neighboring soft tissue. HO is more likely to occur in victims of explosions and creating prosthetics for such victims requires extreme attention to the specific shape of the residual limb.

#### 3.2.4.1 Preliminary results

Figure 3.2 shows an example of a residual limb imaged using CT and segmented with Seg3D. Also visible are the effects of heterotopic ossification, regions of bone that must be taken into account in creating patient specific models of the limb suitable for simulation.

Figure 3.3 shows an example of the trunk of a patient together with the electrode configuration and the resulting simulations of electric field strength along the implanted electrode. The goal of the parameter estimation process is to locate the skin electrodes and apply appropriate electric potential to create uniform electric field along the implanted.

### 3.2.5 Methods and procedures

The main goal of the Center collaboration with this DBP is to develop a comprehensive and validated computational infrastructure to support the creation of patient specific models of the residual limbs of amputees that can assist in the evaluation and treatment by means of osseointegration. This DBP is another example of the image based modeling and simulation pipeline that serves as a central framework of the Center's research and
Figure 3.2: Sample segmentation of residual limb. Segmentation consists of skin (purple) adipose tissue (yellow), musculature (pink), bone (blue), bone marrow (orange) and internal organs (green) (Panel A). Each tissue type was assigned a specific conductivity using SCIRun. A large serpentine-like mass of heterotopic ossification is visible in the medial aspect of the residual limb shown as an axial cross section of the affected limb (Panel B).

development and it will require support from all the TRDs to be maximally successful. To achieve this goal, the Center proposes the following specific aims:

**Aim 1:** Develop segmentation and mesh generation support that is adapted to orthopedic applications like this one, to facilitate the rapid generation of accurate geometric models of amputees and the implants and stimulation electrodes required for these modeling applications.

**Aim 2:** Accelerate the computations required to simulate electric fields and current densities for any selected boundary conditions of implant and skin surface electrodes and provide extensive visualization of the results that include certainty and parameter sensitivity.

**Aim 3:** Develop estimation and optimization strategies for locating skin surface electrodes in ways that maximize the growth potential for electrical stimulation of osseointegration.

To achieve each of these specific aims will require dedicated development and research within all Center TRDs and without the Center, the investigators will be unable to incorporate patient specific modeling and simulation into their research. The alternative is an enormous series of animal experiments, which will, at best, only partially mimic the conditions in actual human amputees. In order to validate and verify both the simulations and the effectiveness of the overall project, there will be animal experiments using a rabbit model with osseointegration implants placed in the hip and then connected with external portable circuitry that provides controlled application of stimulation currents.

Figure 3.4 shows the workflow in animal experiments just beginning. Dr. Bloebaum and his group have developed a rabbit model in which they place metallic implants into and near the femur of the animal, respectively, and then apply a controlled current by means of external, portable electronics. Following a period of
3–6 weeks under constant stimulation, the animal is then anesthetized and receives multielectrode recording needles placed in the tissue near the femur, with which acute measurements provide the distribution of electric potential in the limb. The animal will then be sacrificed, the leg removed, and imaged with CT. Using the steps in Figure 3.4, the investigators, using software from the Center, will create customized models and then carry out simulations to calculate the electric fields from the simulation electrodes and compare those results to the measurements. Histological evaluation of the femur after stimulation will also provide indications of the rate of bone growth into the surface of the implant as a function of the applied electric currents and thus validate the concept of electrically stimulated bone growth and attachment to a metallic implant.

Once validated by this means, the simulation model will then be suitable as a basis to modify electrode locations and stimulation protocols and thus to carry out further animal studies designed to fully mimic the application of this concept in humans. The model will also form the basis of estimation approaches that will seek to optimize within appropriate constraints the parameters of the protocol. We will use sensitivity analyses to determine the critical parameters in the stimulation and determine optimal values for those parameters.

Concurrent with the animal studies will be simulation studies using image data from human amputees, with the goal of translating animal results to the development of viable clinical systems for osseointegration. Here, too, sensitivity studies and estimation approaches will provide a means of predicting optimized electrode locations and stimulation protocols.

### 3.2.6 Impact of the Center resources and technology on the project

Improvements in medical care and evacuation strategies on the field of combat have led to an increased number of veterans surviving disastrous war related injuries. While the improved survival rate is a medical advance, many veterans are returning from combat with amputations that require complex follow-up care, extensive rehabilitation, and expensive prosthetic services. Available documentation has shown that there are now over one thousand warriors with major amputations that have returned from the two most recent major military operations overseas [66]. Of these, approximately 15% of returning warriors have lost multiple limbs and a significant number of returning service men and women have short residual limb for which socket technology is not an option or is rejected by the patient and may be better served with percutaneous osseointegrated implants.

Development of an OIID system to improve rehabilitation regimens and increase bone remodeling is a trans-
Figure 3.4: Workflow for animal validation experiments. The figure shows the workflow for carrying out animal experiments to validate both the concept of the electric stimulation of ossification around the metallic prosthetic implant. Image based simulation begins with CT imaging of the limb under study; segmentation of the relevant tissues of the limb, including implanted electrodes; construction of subject specific model; and simulation of electric field strength.

Biomedical research initiative which can assist clinicians and patients alike. Establishing a standardized mechanism to assess electrical stimulation will help to drive new product development and directly help veteran and warriors. The advantage of the proposed testing protocol is that robust histological and mechanical tests will be conducted and provide the most robust assessment of electrical stimulation in a controlled experiment. Aside from the scientific usefulness, expediting skeletal attachment will directly reduce the length of rehabilitation for veteran and warrior amputees using osseointegration technology. Current load bearing protocols require a waiting period of 12-18 months post-operative until full weight bearing [6]. However, osseointegration will vary between persons [71] and individual rehabilitation programs will be necessary.

The computational support to be developed by the Center for this project will be essential if the application is to progress beyond proof of concept animal studies and really approach clinical application. Patient specific models will be essential, as will sensitivity and optimization studies to determine the critical parameters and their values. The strategies developed for this DBP will also have impact on other projects within the Center and the wider community. The same sort of sensitivity and optimization will benefit the defibrillation DBP and a host of other studies in which electrical stimulation can mitigate pain, control motor control (the Deep Brain Stimulation DPB), or stimulate muscle contraction in the heart and skeletal muscles.

Progress in this project will yield a series of papers as well as potential for product development. The project has already produced conference presentations and a journal article and a second journal article is in preparation. The potential for product development is obvious and funding for the project comes in part from the Technology Commercialization Office of the University of Utah.
4 External DBPs
Part V

Section 6: Collaborators, Service, Dissemination, Training
Part VI

Section 7: Organization and Administration
5 Cited References


