19 Simulation of Cardiac Defibrillation

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(3) Current project funding status: Not currently funded

19.1 Introduction

Implantable cardioverter-defibrillators (ICDs) have become a standard tool of modern interventional cardiology. Many years of development have led to a well-accepted standard of practice for a large and ever-growing cohort of patients. However, despite the considerable level of clinical success, fibrillation and defibrillation remain only partially-understood phenomena. Complicating factors include intra-patient and inter-patient variability in incidence circumstances, anatomy and anatomical pose, state of the tissue, temporal sequence at both larger and finer time scales, etc. and the inherent complexity of both fibrillation events and attempts to effectively disrupt them. Thus, in the interests of minimizing the risk of fatal events, these devices tend to be designed and implanted with a standardized large safety factor, with little tailoring to an individual subject, designed to provide shocks in considerable excess of that needed for defibrillation in most hearts. Experimental and clinical data indicate significant potential for adverse effects of frequent and overpowered shocks, from the cellular to the clinical level. Moreover, the increasing use of these devices, implanted for increasingly long periods of time, has led in turn to two challenges of interest: increasing susceptibility to several modes of failure (e.g., lead breakage), and increasing interest in implantation in special populations, such as children, patients with congenital heart defects, and adults failing standard implant testing.

These increased demands on the devices have spurred renewed interest in re-examination of standard design approaches. For example, in the case of pediatric implantations, devices may be too large to implant in small children in standard locations. Moreover as children grow the resulting change in anatomy may affect device functionality as well as durability. In the case of lead breakage, placement of leads in locations that do not follow the current clinical standard—for instance, subcutaneously rather than in the ventricles—may either lessen incidence or decrease severity of the consequences of a break, or allow easier replacement. In response to these challenges, novel designs, for example fully subcutaneous implantable defibrillators (ICDs), promise to expand access to defibrillation technology substantially (and may even eliminate the need for implant fluoroscopy), but they imply significant changes in the configuration of the applied electrical field and thus, in its interaction with the fibrillating heart.

Thus, current ICD design is suboptimal for many patients considered to be “successfully” treated, and inadequate for special patient populations and subcutaneous applications. However, because departure from established technologies is high-risk, as well as expensive, device design has been very conservative and basic implant strategies have changed little since the technology was introduced. In this setting, the CIBC has been working for the past few years, and is proposing here to continue to work, to develop and employ our tools for robust, patient-specific, image-based simulation and estimation, to the problem of improved ICD design. Specifically in the current DBP we propose to continue and deepen our work on defibrillation modeling in the human torso, with special emphasis on non-standard anatomies and non-standard lead configurations, in collaboration with pediatric cardiologists at Children’s Hospital Boston and Stanford University, a leading researcher on mechanics of defibrillation at John’s Hopkins University, and an adult interventional cardiologist at University of Utah. The goal is to take significant steps toward improving our understanding of effective, robust, and efficient defibrillation approaches, and thus have the potential to impact clinical practice in this critically important and growing area of device-based intervention.

Thus the scientific aims of this DBP are:
Scientific/Clinical Objectives

**Scientific Aim 1:** Increase our ability to confidently predict, via use of a simulation tool, intrathoracic fields produced by variable designs and numbers of implanted electrodes in a variety of poses.

**Scientific Aim 2:** Increase our understanding of how myocardial fiber structure influences the effects of applied electric fields on the fibrillating heart.

**Scientific Aim 3:** Develop design criteria for several specific classes of scenarios of interest, including pediatric ICD implantation and implantation in patients with residual broken leads.

These aims map well to the strengths, interests, and proposed research of the CIBC, which leads us to the following set of objectives for this DBP:

Collaboration Objectives:

**Collaboration Aim 1:** Expand our simulation capacity and efficiency in order to include, for example, more geometric detail and realistic cardiac models than currently supported, dynamic defibrillation protocols, interactive performance, automatic electrode configuration placement, and supported parameter exploration and sensitivity tools. Based on the model estimation tools to be developed under the Estimation TRD (Section 12), we will pay particular attention to balancing prediction accuracy against robustness to geometry and conductivity error and model complexity.

**Collaboration Aim 2:** Enhance current tools for modeling complex myocardial anatomy in defibrillation simulations based on imaging of sample heart specimens and interfacing myocardial simulations of defibrillation with corresponding simulations in the thorax volume.

**Collaboration Aim 3:** Develop algorithms and associated software for predicting good locations to place defibrillation electrodes, given a thorax model and a description of the desired fields at the myocardial interface.

**Collaboration Aim 4:** Validate our modeling and prediction efforts by opportunistically exploiting opportunities for making measurements during clinical implantations.

19.2 Significance

We have four collaborators who are part of this DBP: three clinicians and a leading scientist. Dr. John Triedman is a senior pediatric interventional cardiologist at Harvard Medical School and Children’s Hospital Boston (CHB). He has many years of both research and clinical expertise in many aspects of interventional cardiology. He also has a long track record of research collaboration with CIBC principals Dana Brooks and Rob MacLeod. Dr. Triedman originally brought the idea of pediatric defibrillation modeling to the CIBC’s attention and has been a primary motivator behind the work we have done on this DBP to-date. Dr. Matt Jolley is now a resident at Stanford University but previously was at CHB where he was recruited by Dr. Triedman to work on this project. Dr. Jolley was the primary clinical researcher on the project during his residency. Natalia Trayanova is a Professor of Biomedical Engineering at Johns Hopkins University and the Director of the Computational Cardiac Electrophysiology Lab there. She is widely acknowledged as one of the world’s leaders in the understanding of the effects of applied electric fields on the fibrillating heart and in particular has developed models of unparalleled sophistication and complexity to investigate this phenomenon. Dr. Tom Pilcher is an interventional cardiologist at University of Utah who completed pediatric cardiology and pediatric electrophysiology fellowships at the Medical University of South Carolina in 2008. He has carried out several translational research projects involving cardiac ablation including finite element method (FE) projects.\textsuperscript{730–733}

External defibrillators have long been used as standard therapy for ventricular fibrillation, and ICDs, based on mature foundational technology evolved from anti-bradycardia pacing, have been demonstrated to be an effective, lifesaving technology. Large, well-controlled prospective ICD trials such as AVID,\textsuperscript{734} MADIT-I and -II,\textsuperscript{735, 736} and MUSTT\textsuperscript{737} have revolutionized the concept of sudden cardiac death prophylaxis. These studies have resulted in rapid growth of the patient populations for whom ICDs are indicated, with >110,000 devices implanted in the USA in 2004 only.\textsuperscript{736}

However, an increasingly large, diverse population of patients with ICDs has exposed some of the limitations of this clinical technology. Although mean defibrillation thresholds (DFTs) typically range from 7–11J, ICDs are designed to provide up to 40J shocks to accommodate the 17–24% of patients who require more energetic shocks.\textsuperscript{739–741} Despite this, some patients fail to achieve defibrillation, with 3.4–9.5% exceeding the standard
threshold and requiring special management. Clinical investigators recognize the desirability of reducing shock strength to the minimum needed to reliably (>98%) defibrillate, and nearly 200 papers have been published in the last 10 years on the topic. Excess shock energy incurs significant costs with respect to battery life, device size, and surgical implant techniques, limiting advances in clinical care. Dose related effects of excess defibrillation energy on myocardial Ca\textsuperscript{2+} metabolism, myocardial and ventricular function and overall survival rate are established in animal models, and recent mortality data among patients with ICDs suggests that delivery of unnecessary shocks is associated with elevated mortality. Attempts to reduce the cost and increase the accessibility of ICDs to all appropriate populations are driving the development of simpler, more cost-effective implantable defibrillation systems. These most notably include nontransvenous, subcutaneous ICDs, which can be implanted without the use of fluoroscopy. This development suggests even greater needs for efficient myocardial energy delivery.

Additionally, certain populations of patients are poorly served by current ICD technology. These include children and patients of small body size, and patients with congenital heart disease. Unique difficulties surrounding cardiac defibrillation exist for these groups (Fig. 19.1), including high rates of lead failure, particularly in children and adolescents, frequent inappropriate therapy, mismatch of device and lead size to the child’s body, and the effects of somatic growth and long life expectancy. Lead failure in particular can lead to either substantial risk of morbidity or mortality if extraction is pursued, or substantial change in effective applied fields if extraction is not pursued or is not fully successful. These data indicate that “tuning” of ICD parameters to patient-specific factors is critical to further development of this technology.

Figure 19.1: A wide variety of nonstandard ICD implant locations has recently been reported in literature. These views demonstrate inferior caval, subcutaneous and intrapericardial electrode locations in three pediatric patients.

The current state of defibrillator development is only weakly informed by recent advances in the electrophysiology of defibrillation. Energy dosing and electrode placement for current ICDs are the result of conservation of anti-bradycardia pacemaker design and the serendipitous availability of battery and capacitor technology capable of providing adequate defibrillating shocks in standard configuration, determined empirically from clinical observation informed by a general understanding of the effect of electrical stimulation on the heart, and subsequently validated in standard adult torsos by experimental and clinical study. Any information about complex mechanisms behind defibrillation failure is lost to the clinician or engineer in the binary nature of the DFT calculation. The adoption of biphasic shock waveforms is an example of this lack of translational integration; clinical observation of efficacy preceded and drove more basic research to resolve competing scientific explanations for the observation.

Many patients who failed with standard transvenous defibrillation subsequently responded successfully to modification of the shock vector, achieved by placing an additional electrode or electrode array subcutaneously near the cardiac apex. Subsequently, a wide variety of novel and innovative approaches to ICD implantation have been demonstrated to be clinically feasible in children, congenital heart patients and adult patients with normal anatomy. These approaches have generally utilized “off-the-shelf” technology in untested ways. Little data is available to guide the specific application of defibrillation strategies in these patient groups.
Clinical studies are difficult due to ethical and practical considerations. In summary, because the clinical application of ICD technology is rapidly outstripping the scientific bases for its application, and because this technology is further being deployed into clinical situations for which it has been neither designed nor extensively validated by clinical experience, there is now a pressing need for alternative approaches to technology development, therapy planning and clinical research in the field of cardiac defibrillation, that are both flexible and incorporate our increased knowledge of defibrillation mechanisms.

19.2.1 Previous efforts to model defibrillation in torso models

Finite element (FE) modeling has been used by several investigators to predict the intensity of an electrical field in a conductivity model of the thorax, as well as effects of defibrillation on the myocardium. These earlier studies, based on electrically static models of the chest, have been limited by computational constraints on model complexity and flexibility, limited size range of subjects, lack of flexibility with respect to electrode placement, and an overly simplistic assessment of the interaction between the defibrillating field and the myocardium. However, they have clearly established the potential predictive value of this approach. Thoracic finite element models have been validated electrically using both direct shock measurement and application of high-frequency trickle current. Parametric analyses have demonstrated the sensitivity of such models and several have been able to demonstrate some degree of concordance with clinically determined DFTs and interactions between cardiothoracic anatomy and lead geometry. However, all predicted only the static thoracic electrical field induced by the shock, and relied on inference to predict the DFT.

19.2.2 Biophysical models of cardiac defibrillation

Understanding the interaction of the applied electric field with the fibrillating myocardium has been the subject of intense research and debate. Over a decade ago, bidomain simulations demonstrated that the membrane response in the vicinity of a strong unipolar shock involved simultaneous occurrence of positive (depolarizing) and negative (hyperpolarizing) effects on the cellular membranes of cells in close proximity. This finding of “virtual electrode polarization” (VEP), which constitutes the essence of the effect of the shock on the myocardium, has been documented in experiments and supported by simulations involving shock delivery from various electrode configurations. Biophysical models have played a pivotal role in the detailed analysis of the formation of VEP. They have shown that tissue structure, particularly fiber architecture, is responsible for the generation of VEP and for its shape, location, polarity, and intensity. Furthermore, in conjunction with optical mapping studies, they have demonstrated that the cellular response to VEP depends on VEP magnitude and polarity and the state of the cell at the time of shock delivery. A shock succeeds in extinguishing fibrillatory wavefronts and not initiating new reentry if excitations manage to traverse the shock-induced excitable areas before the rest of the tissue recovers from shock-induced positive polarization. Clearly, accurate prediction of the generation of VEP and subsequent propagation of post-shock activations is necessary for the accurate prediction of shock outcome, and requires explicit representation of both the electrophysiological properties of the myocardium as well as the myocardial geometry and fiber architecture.

19.2.3 Overview and significance of the proposed approach

We hypothesize that large-scale structure such as heart geometry and fiber architecture combined with the specific voltage field geometry created by the electrode configuration within the individual patient torso are the primary clinical determinants of shock success. We will develop simulation tools designed to allow integration of these factors. The prototype components of this tool have already been assembled by collaborative efforts of CIBC and Dr. Trayanova’s group.

The needs of Collaboration Aim 1, on building better forward models, will be served by the meshing tools to be developed under the Image-Based Modeling TRD, the forward modeling tools, including GPGPU acceleration, to be developed under the Simulation TRD, and the model design tools to be developed under the Estimation TRD. Collaboration Aim 2, on building models of imaged hearts, will be served through segmentation and meshing tools from Image-Based Modeling. Aim 3, on optimal defibrillation electrode design, is a prime motivator for work in optimization of bioelectric stimulation in the Estimation TRD. And Aim 4, on validation, will require tools for comparing body surface potentials based on software closely tied to the estimation work in that same TRD. Much of this work is closely tied to other efforts towards “personalized medicine”, in the guise of software pipelines for building individualized computational models and applying them to solve translational
biomedical problems, that is a, if not the, central theme of this CIBC renewal.

19.3 Rationale and preliminary work

We have arranged our presentation of preliminary results according to the Collaboration Aims outlined above.

19.3.1 Modeling of defibrillation fields in the human torso

In order to simulate the efficacy of ICD lead placement for pediatric patients of various ages, we generated a series of detailed torso segmentations in collaboration with Drs. Jolley and Triedman. These segmentations were based on acquiring CT scans of patients which were obtained for clinical indications unrelated to this project. One of these scans and its subsequent segmentation into different tissue types is given in Figure 19.2A.

![Figure 19.2: Panel A: A volume rendering of the CT image used for generating the defibrillation models, overlaid with the segmentations of blood, heart, lung, and bone. Panel B: Isopotential surfaces reflecting the simulated potential field inside the torso due to defibrillation shock between a coil electrode and the ICD can. The closer the isopotential surfaces are together, the higher the potential gradients are in a certain region.](image)

Together with Drs. Triedman and Jolley, we also generated a database of electrode lead configurations that they determined as clinically feasible sites for lead implantation. This database is based on the anatomical segmentations of the various CT scans, and contains a wide variety of implantation scenarios including subcutaneous, epicardial, and intravenous leads as well as classic locations for the defibrillator can. Additionally we included locations used in pediatric patients, e.g., in the lower abdomen. The database to date consists of about 400 different configurations placed inside four different computational anatomical models. The database was generated by our collaborators using SCIRun networks we designed that rendered a 3D image of the anatomy in which leads could be visually modified using anatomical landmarks as visual references for lead placement.

The initial prototype that we generated for this project used these segmentations and the lead configuration database to build FE models using hexahedral meshes with local refinement. Solving the quasi-static bioelectric field problem in SCIRun, we were able to estimate the efficacy of each lead configuration by assessing how much of the myocardium received a potential gradient of 5 V/cm or more due to the defibrillation shock (based on what is known as the Critical Mass Hypothesis). An illustration of the resulting potential field is given in Figure 19.2B. We published a study in Heart Rhythm [776] that showed that for one case of the model where we had data obtained during a actual implantation surgery for that individual, in which different lead configurations were tested, relative efficacy was consistent with the simulation predictions. The simulations also showed that there may well be more effective lead locations than the ones currently in use.

We are currently finalizing a follow-on study that will include a far larger database than the cases considered in this first report. This study focuses on trends in efficacy, along with the use of subcutaneous leads to reduce
Since our initial results using hexahedral meshes, we have also generated defibrillation models based on tetrahedral meshes that more accurately model sharp changes in conductivity between, for instance, the myocardium and blood. An example of a newly generated tetrahedral models is shown in Figure 19.3. The figure depicts the smooth surfaces between the different model compartments. The tessellation of the triangles on the surfaces was optimized such that the tetrahedralizer could generate a mesh with good mesh quality metrics (such as the scaled Jacobian). We have also verified that the current tetrahedral mesh models produce results that closely correspond to values found with our initial approach. We have now updated our software tools to work with either approach.

We have also expanded our tools to include “floating” electrodes, i.e. models for electrode leads that are fracture. These fractured leads warp the applied field since they have a much higher conductivity than the surrounding tissue. We have added new modules into the SCIRun infrastructure that modify the original defibrillation models and permit the solution to include the effect of these additional broken leads. In collaboration with Dr. Pilcher, we have started to map these scenarios and we have generated a first example of such a configuration which shows that the induced thoracic field can indeed be significantly altered by the presence of a broken lead. The current project is focused on visualization of these differences; a quantitative study will follow soon.

Finally, we have recently generated an implementations of our electrode configuration software that does not depend on Matlab, instead implementing all computations directly into the SCIRun framework. The new electrode lead configuration module now also allows the user to alter the shape of the electrodes, which will support the planned work by Dr. Jolley exploring even more unconventional defibrillation lead configurations.

19.3.2 Modeling of defibrillation in the fibrillating myocardium

Dr. Trayanova’s team has published many simulation studies elucidating the mechanisms by which an electric shock interacts with the myocardium. In recent studies they have further shown 1) their ability to simulate shock-induced vulnerability and defibrillation in biophysically and anatomically detailed bidomain isolated heart models, using clinically relevant shock waveforms, and 2) the predictive power of such models and their ability to dissect the mechanisms that underlie shock failure.
Figure 19.4: A: Model (bottom) and experimental (top) preparation with uniform-field shock electrodes in the perfusing bath. B: Vulnerability areas (VAs) for RV- and LV- shocks in experiment (top) and simulation (bottom). In the top panel, vertical axes represent probability of arrhythmia induction in 5 experiments. In the bottom panel, dark areas represent VAs, and asterisks denote episodes of shock delivery. Shock strength (SS) and coupling interval (CI) are calculated as deflections from the upper limit of vulnerability (ULV) and CImax. C: Optical map of shock-end potentials from one rabbit and the corresponding simulated potential distribution. The white square in the simulation panel outlines the location of the optical field of view in the experiment. D: Evolution of simulated post-shock activity for RV- (top panel), and LV- shocks (bottom panel). White arrows represent direction of propagation.

In a collaboration between Dr. Trayanova's lab and the lab of Dr. Efimov at Washington University, St. Louis, Rodriguez et al. used optical mapping experiments and 3D bidomain simulations to investigate the role of structural differences between LV and RV in vulnerability to shocks in normal rabbit hearts. Although effects of shock strength and waveform on vulnerability have been extensively documented, the specific contribution of ventricular anatomy to shock-induced virtual electrode polarization (VEP) and propagation and thus, to shock outcome, has never been quantified due to lack of experimental methodology capable of mapping 3D electrical activity. In this study, the ventricles were paced apically, and uniform-field monophasic shocks of reversed polarity were applied over a range of coupling intervals (Fig. 19.4, Panel A). Changing the direction of the externally-applied field (RV- or LV-shocks) significantly altered the shape of the vulnerability area (areas on a 2D grid that encompass episodes of reentry induction for various shock strengths and coupling intervals, i.e., shock timings), and the probability of arrhythmia induction. In both simulations and experiments, there was little or no dependence observed of post-shock arrhythmogenesis on coupling interval for RV- shocks. For LV- shocks, probability of arrhythmia induction was higher for longer than for shorter coupling intervals (Fig 19.4, Panel B). After demonstrating correspondence to experimental data regarding the epicardial shock-end transmembrane potential pattern (Fig. 19.4 Panel C), simulations proceeded to show that these differences in vulnerability areas stem from the fact that field reversal results in relocation of the main post-shock excitable area from the LV wall (RV-shocks) to the septum (LV-shocks) (Fig. 19.4, Panel D). The excellent match regarding shock-induced VEP, post-shock propagation patterns, shock outcome, and upper limit of vulnerability values between experimental data and simulation results obtained with bidomain models demonstrates that fiber structure and organ geometry are the main determinants of shock outcome; it is the fiber structure and organ geometry that generate large intramural post-shock excitable pathways through which the post-shock wavefronts can propagate. Most importantly, shock outcome and the type of post-shock arrhythmia depend on the anatomical location of the intramural post-shock excitable area formed by shock-induced de-excitation of previously refractory myocardium.

In additional simulation studies, Dr. Trayanova and her group have also extended the above findings and proposed a new theory of post-shock propagation and shock-induced arrhythmogenesis that unifies all known aspects and findings regarding the electrical behavior of the heart following monophasic and biphasic shocks. All their findings support the notion that to represent through simulation realistic fibrillation and defibrillation requires heart models with resolution on the order of 100–400 µm that have accurate representations of fiber structure. For their research to continue, they need access to efficient and powerful software to create such models as well as the associated MRI image data from real animal and human hearts. The Center is well
placed to work together with Dr. Trayanova to fulfill these needs.

### 19.3.3 Validation of modeling during clinical implantation

To further validate the defibrillation model we have developed, we began a collaboration with Primary’s Children Hospital at the University of Utah. The goal was to measure the potential distributions on the body surface generated by the defibrillation shock of the ICD. Clearly, one of the few situations in which an ICD is discharged in a subject under controlled conditions is during the implantation procedure. Because the clinician needs to ensure that the device is programmed to generate a shock that is sufficiently strong that it can be confidently expected to defibrillate the heart, the device is tested several times during the surgery while the patient is still under anesthesia. Our goal was to measure body surface potentials during these test shocks.

We have adapted a system that was optimized for body surface potential maps of intrinsic cardiac signals by adding a voltage divider to the sensor system in order to reduce the measured potentials down to the range of 1000 Volts. We also adapted the lead system to be easily applicable during implantation surgery; in particular we need to be able to measuring body surface potentials over a large portion of the torso. In addition to the body surface potentials we obtained a full torso MRI scan of each of the patients. So far we have measured these body surface potentials in three cases. Two were used to properly design the experiment, in particular to optimize the measurement procedure during surgery and determine the MRI protocol to use. The third case in the series produced segmentable MRI scan and good quality body surface potentials as well as recordings of lead locations. Thus we have completed a visual comparison between the individualized computational defibrillation model built from the segmented MR image and the measured body surface potentials. Figure 19.5 shows this first visual comparison.

As the current measurement system allows for the measurement of only 32 leads, and because we are limited to particular areas of the body surface since a relatively large sterile field is needed for the surgery, we modified an existing method to interpolate a body surface potential map between the various measurement lead locations. We used simulations from the study with Drs. Triedman and Jolley to generate a training set that included defibrillation shocks from a variety of electrode locations. From these results we selected the lead locations within the accessible portion of the body surface that we were best suited for reconstruction of the body potentials using a mathematical procedure. The measured body surface potentials shown in Figure 19.5 were based on this estimation technique. These first results were presented at Computers in Cardiology 2009.

![Figure 19.5: Validation of our defibrillation model: The left panel shows body surface potentials in the patient specific model, while the right panel shows body surface potentials interpolated from the measurements during the surgery.](image)

### 19.4 Methods

We organize our plan for this DBP according to the Collaboration Aims we plan to achieve.
19.4.1 Collaboration Aim 1: enhanced simulation models

Achieving this aim will be a prime outcome of the integrated simulation pipeline involving both the segmentation and meshing efforts described under the Image-Based Modeling TRD and the bioelectric forward simulations, especially with GPGPU acceleration, to be developed under the Simulation TRD. Indeed this DBP has been one of the key drivers for the first of these efforts for the past several years, as is evidenced by our publication record on this project. In the area of implementation of FEM computation on GPGPUs as described in Section 11, there is a perfect match between the goals there and the needs here, so the transition of our defibrillation simulations onto the tools resulting from that research will be seamless.

We have also begun to study which organ systems are most important, and which least important, to include in our geometric / anatomical forward models. In Section 12 we describe a sequence of research and development efforts on more sophisticated methods for studying this problem, as well as the conceptually related problem of which organs need to be modeled with reactive components when realistic shock waveforms are employed. This DBP again was a key driver behind creating that plan and will be a key beneficiary of the proposed work.

Finally, we currently have a software tool for such simulations that allows users to choose electrodes from a pre-defined library, move them around as desired in the 3-dimensional volume, and then request a simulation result. Our software refines the FE mesh according to the new electrode position and then computes the result. Although this tool is already of sufficient quality for use by clinicians (Dr. Pilcher is already a regular user), we will undertake further software hardening to make it even more appropriate for use in translational settings.

19.4.2 Collaboration Aim 2: Building tools to model of anisotropic myocardial anatomy

To achieve this aim, we will develop the workflow and software necessary to carry out image processing, segmentation, and mesh generation of high resolution finite element models of adult and animal hearts scanned for the studies. We will then, starting from the same image set, compare the results of segmentation and mesh generation approaches using the Center tools (Seg3D and BioMesh3D) to the results achieved by the Trayanova lab using their own tools. We will not only compare the segmentations and meshes from a geometric perspective, but also evaluate the impact of any differences on the outcome of simulation of fibrillation and defibrillation as carried out on the Trayanova lab.

The source of scans for human models will be autopsy specimens obtained by Dr. Triedman from patients under an existing IRB protocol at the Children's Hospital Boston. They will be from patients of various ages and sexes whose cause of death was not cardiac in nature. Between 10 and 15 such studies are anticipated in the first two years of the project with the initial focus on structurally normal hearts. In subsequent years of the project, Dr. Triedman and his team will extend this approach to hearts with known myocardial pathology, including ventricular hypertrophy, dilation, and scarring.

By detecting the anisotropic diffusion of water exerted by the microscopic environment of the myocardium, diffusion tensor magnetic resonance imaging (DT-MRI) has emerged as a powerful extension of traditional MRI. Strong evidence exists indicating that the preferred direction of water diffusion coincides with the local myocardial fiber orientation. The University of Utah is well equipped to perform DT-MRI scans of these hearts, with a dedicated Bruker Biospec 7.1 T horizontal-bore MRI with dual sets of gradients and an upgraded power supply capable of 30 G/cm and 60 G/cm peak gradient strength. The total scan time for all scans is estimated to be 18 hr. In post-processing for DT-MRI, we will compute diffusion tensors on a pixel-by-pixel basis via non-linear least squares fitting, and then take the eigenvector corresponding to the largest eigenvalue (i.e., the direction in which water diffusion is strongest) as the local fiber orientation. From the DT-MRI images, it is necessary to extract these local fiber orientations, for which we will use the methodology of "cardiac myofiber tractography" previously described by Helm and McVeigh. In order to create models with the essential fiber structure information, all steps in the model generation pipeline will have to extract, preserve, and utilize the fiber information. We have carried out two such studies to date, as described in Section 19.3.

The goal of anatomical segmentation is to identify the appropriate tissue designation for each voxel in the data set according to its functional and electrical properties. We will first use Seg3D to apply several different methods of image intensity correction and equalization that are suitable for MRI, and then we will apply both manual and automatic segmentation algorithms in three dimensions. We will identify as many tissue compartments as the images reproducibly provide; identification of as many regions as possible is a motivation for acquiring both T1 and T2 weighted scans during imaging as each is sensitive to different tissue characteristics.
The next step in creating the geometric models for the heart is to create a volumetric polygonal mesh from the segmented image data and assign local fiber orientations from the DT-MRI scans to each element of the mesh. The special requirements of this mesh generation include a close fit of the element faces to the epicardial and endocardial boundaries. Dr. Trayanova’s group will achieve such a mesh using an octree-based meshing method that produces boundary-fitted, locally-refined, conformal meshes with one or more boundary layers. This method begins with a background mesh consisting of the voxels of the image data and then creates a hierarchical structure that organizes the voxels based on the tissue type and the boundaries between different tissues. Nodes at the tissue boundaries then define surfaces, which are then smoothed to ensure close conformance to the actual tissue boundaries. The BioMesh3D system uses a slightly different system based on first spacing particles over the surfaces involved and then creating closely fitting surfaces (See Section 9.3.2). Both approaches then fill the regions defined by the surfaces with elements (hexahedra or tetrahedra), and again apply smoothing to create elements that efficiently fill the volume and maintain the balanced aspect ratios that result in numerically stable finite element solutions. It is possible to select the average resolution of the mesh and thus adjust the level of detail automatically, i.e., so that no elements are grown into structures that are below the chosen resolution.

In a final step, tissue tags and fiber orientations from the DT-MRI will be transferred, by interpolation, from the original structured grid (the voxel grid) onto the tetrahedral mesh grid so that each element of the mesh has a single tissue type and fiber orientation. Dr. Trayanova’s method ensures that fiber orientations are parallel to the cardiac surfaces in all elements at a surface layer to avoid spurious shock-induced currents.

Once we have such models, we will begin to explore methods to connect the detailed anisotropic myocardial simulations carried out in Dr. Trayanova’s lab with our existing torso volume simulations. Details of how this will be carried out, and of which work will be done at John’s Hopkins and which at CIBC, are difficult to determine at this point as they depend on computational burdens and modeling efficacies that are unknown in advance, and they also depend on the degree of computational speedup we will be able to obtain with our GPGPU methods described in Section 11.

19.4.3 Collaboration Aim 3: Prediction of optimized defibrillation scenarios

As described at some length in the Estimation TRD, we plan to pose the problem of suggesting effective and efficient number, locations, poses, sizes, and even waveforms for defibrillation electrodes, given an FE model and desired fields on the heart surface, as an inverse problem. This is a “non-standard” type of inverse problem that will require new methods to be developed, as discussed in that TRD description. Once again, this DBP is the prime driver behind that work and indeed the initial development will specifically use requirements and constraints, as well as FE models, derived from these defibrillation scenarios. Thus we plan to pursue this Aim as a direct consequence of that proposed TRD research.

19.4.4 Collaboration Aim 4: Model validation

Given the limited resources available, we plan to continue our current effort to validate our defibrillation models by working in collaboration with Dr. Pilcher to measure potentials at available locations on the body surface during implantation procedures. We then will compare those measurements to our model predictions. We currently only choose the maximum voltage to compare, leading to scaling discrepancies in the comparison, and leaving out the full spatio-temporal nature of a more precise comparison metric. In conjunction with estimation tools to be developed in the Estimation TRD, we will study a number of standard and novel metrics based on both statistical and deterministic interpolation techniques, in space, in time, and jointly in space and time. From the TRD point of view the goal will be to evaluate the metrics for translational relevance; from the point of view of this DBP the goal will be to measure the accuracy of our model. In particular we will study which aspects of the model seem to be most directly linked to measurement discrepancies and attempt to refine our model building tools to lessen the specific sensitivities which we will discover during this validation effort.

19.5 DBP interaction and management

We have a several year long track record of active and successful collaboration with Drs. Jolley and Triedman, with a publication record that indicates our success at getting this collaboration underway. Dr. Pilcher’s collaboration with CIBC, although relatively recent, has already produced meaningful results and there is clearly strong motivation on both sides to continue. The proposed collaboration with Dr. Trayanova is a mature effort among
several established investigators who themselves each have a strong track record of inter-institutional and interdisciplinary research efforts. Indeed we have already transferred initial data from CHB to Utah to John's Hopkins and then transferred the resulting meshes back to Utah for visualization and inspection. We anticipate that our current practice of frequent electronic contact, timely video or telephone conferences, and occasional visits, will continue and indeed continue to be sufficient to ensure steady progress. As with all DBPs, status, progress, and work assignments will be regularly reviewed at our weekly Executive Committee and Management Team meetings.

19.6 Impact

The work proposed in this DBP can confidently be expected to have a significant impact in the field of ICD electrode design and implantation. As described at the outset of this DPB section, we are currently seeing a conjunction of broader use of ICDs, on a more diverse population in terms of age, anatomy, clinical indication, etc, and recent academic and industrial attention to the problem of lead failure. All of these factors make the development of a simulation package for “personalized” patient-specific defibrillation modeling of broad visibility. In addition, we expect our tools to have unprecedented flexibility to accommodate novel lead designs and unprecedented ability to compute results in complex anatomical scenarios. Thus we indeed believe this will be the right tool at the right time. Indeed this assertion is supported by conversations and interactions we have had as a group with two of the major device manufacturers over the past year. Neither is ready to invest in a large-scale academic research effort, but both made it clear that they have great interest in the availability of a tool with the capabilities we plan.

Finally, the problem addressed in this DBP has close parallels with the proposed DBPs on brain stimulation, with Dr. Butson, and bone stimulation, with Dr. Bloebaum. We fully anticipate a synergistic interaction, at the technical, software, and even clinical, levels, among these three DBP efforts, and associated efficiencies of effort for the Center.