

Progress Report

Software Infrastructure (BioPSE)

To render support for our collaborators we are integrating the algorithms and software advancements for each project into a single Problem Solving Environment, called SCIRun/BioPSE. This allows for sharing progress in one project with the others and helps with maintaining synergy between the various projects. In order to be able to support the projects of our collaborators, significant changes to the SCIRun/BioPSE framework have to be made in order to be able to add new functionality and allow for creating new stand-alone applications that support the research of our collaborators. The architecture of the SCIRun/BioPSE framework is being improved in several ways:

(1) In order to improve the usability of software tools we like to provide stand-alone applications targeted at the science of our collaborators. In previous years collaborations were supported with the creation of the so-called PowerApps, these applications were running in the scripting language TCL and created a simple front-end to the SCIRun/BioPSE software framework. However experience with these tools has taught us that although the PowerApps provide a reasonable interface for doing science, having a dataflow network underneath was a serious limitation. In order to generate a more flexible framework, we are currently in the process of splitting the SCIRun/BioPSE code in such a way that we can build fully self contained applications on top of our framework. This will allow us to generate applications that are more interactive from a user perspective. We made progress in reworking the core of SCIRun/BioPSE so it has an abstract algorithmic layer that can be reused in several projects and will allow us to change the graphical user interface on top of the framework. This algorithmic layer has been designed and about a third of the algorithms have been ported into this layer.

(2) In order to provide better numerical stability, the core of all our mesh classes has been rewritten and basis functions have been added, which describe how geometry and data is to be interpolated between nodes. This addition will enforce a coherent interpolation scheme underneath the SCIRun mesh classes, which is necessary for reliable numerical field calculations. This change forced us to rewrite the finite element code and make it more general so it can now be applied to every element type in the SCIRun/BioPSE framework, which is important for doing 2D simulations or simulations based on hexahedral elements. This framework was designed in such a way that it not only provides a proper interpolation scheme for linear elements, but as well for higher order elements, both Quadratic Lagrangian schemes as well as Cubic Hermitian schemes have been implemented.

(3) We added new functionality to the SCIRun/BioPSE framework. With the new focus on collaborations it became clear that we had significant gaps in the scope of our software. The most requested feature is a simple pipeline that lets a scientist take an anatomical image and build a model out of this. Hence several projects are underway to fill these gaps in functionality: (a) a new segmentation system is being developed, (b) mesh generation tools have been added, (c) model editing tools have been created. A new segmentation application is being developed called BioPainter, which is a visual interface to the Insight Toolkit library. In order to have better support for mesh generation in SCIRun we added a bridge to the TetGen software (An open source library for conforming Delaunay tetrahedralization) and bridges to the Verdict library (A tool to verify mesh quality) and the Mesquite library (A tool for optimizing the computational grid to get better quality elements) both developed at Sandia National Laboratories. In order to support better model editing a new package called ModelCreation was added, which includes a series of tools for editing and manipulating model parameters. In order to support the creation of cardiac models for the collaboration with Dr. Henriquez, an additional package called CardioWaveInterface was created, which contains a set of specialized algorithms to support the model editing needed and algorithms to export the model so it can be used by the CardioWave software developed by the group of Dr. Henriquez.

(4) A drawback over the years has been that our software does not run on Windows and that it is hard to install. To improve this a SCIRun version for Windows has been created. Besides support for Windows, we upgraded SCIRun to support the latest version of the gcc compiler (version 4) and made it available for the latest version of the Macintosh OS X operating system. Furthermore, the make system is currently being rewritten to use CMake, and the number third party libraries we rely on, has been made smaller. All these improvements are aimed at creating a system that will be far easier to install.

Image Processing and Geometric Modeling

The focus in the image processing and geometric modeling core has been threefold: (1) improving the statistical shape analysis tools, (2) creating an interface for doing operations on 2D or 3D data sets ranging from segmentation to shape analysis, (3) creating tools that will transform segmented images into meshes that can be used for simulations.

(1) At the Center for Integrative Biomedical Computing and Scientific Computing and Imaging Institute, we have developed a non-parametric method for extracting dense sets of correspondences between shapes using a particle system, where particles are distributed across the ensemble shape surfaces in an optimal

configuration. The optimal distribution is iteratively computed to minimize an energy functional based on the information content of all particle positions. This energy functional seeks to simultaneously maximize entropy of particle distributions on individual shape surfaces while minimizing entropy across the entire ensemble. The resulting distribution favors a compact ensemble representation, but also a uniform distribution of particles across each surface by maximizing the entropy of each individual shape distribution. Since particle positions are not tied to a specific surface parameterization, the method operates directly on volumetric data, extends easily to higher dimensions or arbitrary shapes, and provides a more homogeneous geometric sampling and more compact statistical representations. We already have some promising results using this method (Cates et al., 2006) and are actively applying it to data from Capecchi laboratory (primary collaboration) to characterize shape variation of the mouse bones.

(2) A first version of a new general-purpose volume segmentation application has been developed, called BioPainter. This application is constructed using SCIRun/BioPSE visualization components, custom OpenGL code, and the Insight Toolkit library for image IO, image processing and image segmentation and registration. This application is the first stage of an integrated suite of tools designed to go from raw image data to models for simulation, visualization, and quantitative image analysis. A distinguishing feature of BioPainter is that it manages volume data as a set of 3D layers. This is similar to how standard paint programs such as Photoshop, which are limited to 2D data.

(3) In order to allow for a constraint mesh generation in the SCIRun/BioPSE framework we added a series of tools for creating meshes: we added a bridge to the TetGen library (a boundary constrained Delaunay tetrahedralization library), developed by the Research Group of Numerical Mathematics and Scientific Computing Weierstrass Institute for Applied Analysis and Stochastics in Berlin; we added links to both the Mesquite library (Mesh optimization) and Verdict library (Evaluation of mesh quality) developed at Sandia National Laboratories. These tools are the first in series of tools we plan to incorporate into the SCIRun/BioPSE framework in order to help our collaborators with the creation of spatial models for their simulations.

Mathematical Modeling and Simulation

Besides bioelectric fields, the scope of the mathematical modeling and simulation core has been broadened to include physiology of the cell and membrane and also the mechanistic approaches beyond electrophysiology to include support for biomechanics as well as the biophysics of diffusion and transport systems. Progress has been made in three areas of simulation: (1) in multi-scale cardiac

simulations, (2) in the localization of sources in the brain and (3) in wave-front base inverse reconstructions of epicardial potentials.

(1) We are using the area of simulating the behavior of cardiac tissue as example for developing the tools needed to construct the models. The process of performing multi-scale simulations of cardiac tissue is typical of many biological simulations in that it includes four typical components: (1) creating the geometric model of the tissue, (2) defining the behavior to be simulated at the appropriate spatial and temporal resolution, (3) setting specific conditions and running the simulations, and (4) visualizing and analyzing the results of the simulation. In this part of the project we focused on integrating only the first two parts of the simulation pipeline, i.e., the creation and definition of a simulation, using interactive tools with strong support for visualization of the model as it develops. We have also made progress on the tools for visualization and analysis of simulation results. For the simulations performed we used a geometric model based on a more generalized description of cardiac tissue. The particular model we have developed consists of volumetric geometries to describe the electrical potential in the intra- and extracellular spaces of the myocardium, and consists of surface elements to describe the membranes and intercalated disks that separate the different compartments in the model. To carry out the tasks of grouping elements of the model and assigning general parameters, we created a new package in the SCIRun/BioPSE framework called ModelCreation. Once all the spatial parameters are defined, the specific geometric model itself needs to be generated. For this task we have created a new package within SCIRun/BioPSE called CardioWaveInterface. To test the scheme of building tissue level models, we implemented two geometrical models of tissue: (1) a simple brick-like architecture of a strand of twenty myocytes, and (2) a more realistically shaped model consisting of a strand of 2 by 2 by 18 cells. We have also used these models to address a persistent question in cardiac electrophysiology related to the response of heart tissue in the face of a shortfall in blood supply, which is known as myocardial ischemia. Two processes are known to occur at the onset of ischemia, extracellular potassium concentration rises and the extracellular space collapses, because of a shift in fluid from this space into the cells and the capillaries. Investigators have shown in cellular preparations that the effect of increased potassium in the extracellular space increases the propagation velocity of the action potentials in the tissue. This tissue-level response, however, is not observed in experiments with animal hearts. Hence we first investigated the effect of the collapse of extracellular space that also accompanies ischemia by means of simulations using geometric models with varying extracellular spaces. The results showed that by setting physiological realistic simulation parameters, the two effects cancel each other so that there is no net change in conduction velocity. Results from these studies have been presented at two conferences.

(2) Another project that is underway to strengthen the development of tools is the study of conductivity uncertainty in the localization of current dipoles in the brain from scalp measurements of electric potential or magnetic field. Such dipoles are realistic representations of focal electrical activity among bundles of nerves in the brain, such as those that can arise in epilepsy. In this particular study, we have developed a global optimization method based on simulated annealing within the NeuroFEM brain source localization toolbox. The goal of the method is to search for the global minimum, which represents the dipole source location, of a cost function based on combinatorial optimization and what is known as the Metropolis algorithm. In order to evaluate the effect of conductivity choice on solution accuracy, we have recently implemented a new source localization method known as conductivity fitting within NeuroFEM. Conductivity fitting adds the values of conductivities as free parameters chosen from a predefined discrete set of conductivity values. This method is under validation study with a four layer realistic head model and the results will appear on a conference presentation later this year.

(3) We have recently reported two recent attempts to incorporate spatio-temporal constraints in the context of wavefront propagation. The first used the Kalman state-estimation formalism in the context of a constraint based on wavefront propagation. This approach is in principle like previous methods using activation times as the source representation in that it considers the arrival time of the wavefront at each point on the surface as the unknown values to reconstruct. The novel aspect is that it uses a non-linear state evolution model built on phenomenological studies of canine epicardial data, along with fiber directions drawn from the Auckland heart, to propagate the wavefront on the epicardial surface. A second model, also built from study of canine epicardial data, maps the wavefront location to a potential distribution; the latter is then used with a standard forward solution to relate the wavefront location at any time instant to the body surface potential measurements. The second approach uses a regularization constraint based on a non-linear mapping of the previous time instant solution to a wavefront-based model; this constraint is then used in a standard Tikhonov inverse solution to calculate the solution at the current time instant. We have shown both methods to have significantly improved localization and extent of reconstructed wavefronts in simulations with cardiac data.

Scientific Visualization

During the last 12 months we have carried out both fundamental and applied research to improve and extend the visualization tools available to the collaborators of the center:

(1) In collaboration with Dr. Bruno Taccardi (Cardiovascular Training and Research Institute, University of Utah), we created the first visualization of the full sequence of intramural activation and repolarization in canine ventricles. To achieve high visual quality we combined remeshing techniques with smooth interpolation schemes.

(2) We devised a new efficient algorithm that computes the shadows of large-scale isosurfaces extracted at interactive frame rates. The added visual cues significantly improve the interpretation of depth and shape of the complex geometries and permit a more effective and reliable analysis of the resulting images.

(3) We also applied advanced vector visualization techniques to enhance the representation of bioelectric fields. In particular we have investigated the benefits of stream surfaces and texture representations to assess the influence of conductivity anisotropy of the white matter on the solution of the forward problem. Our visualization results helped elucidate the impact of the modeling of this anisotropy on the accuracy of the solution of the inverse problem for source reconstruction in the brain.

(4) In collaboration with Dr. Zaitsev (Cardiovascular Training and Research Institute, University of Utah), we created visualizations of the phase of the action potential in ventricular fibrillation and added tools to the SCIRun/BioPSE framework to extract wave fronts and singularity points at the epicardium.

(5) New tools have been added to do a probabilistic classification of an entire data set. This method allows for visualization of uncertainty and puts control over the decision-making into the hands of the scientist.

(6) The capabilities of Map3D were extended to better support the needs of our collaborators. Map3d now supports the display of both potentials (time signals) and activation times (single map), or any other time instants derived from the time signals. This display can occur in the form of an overlay, in which potentials appear as color-shaded surfaces and the activation times as black isochrones. We also improved the multi-surface display features and it is now possible to group surfaces and apply colormaps and scaling to a group of surfaces.

Collaborations

Collaborations are a key element in the new setup of the center. We have made progress in several of the collaborative projects:

Computational tools for multiscale heart modeling (Collaborator Dr. Henriquez)

For this project we created two new packages, one for model creation and model editing tools, and one for interfacing with the CardioWave software developed by Dr. Henriquez' group. We modified the CardioWave software so it will now allow for tissue level simulations using an adaptive time scale and using the finite element method based on unstructured meshes. Using these new packages and modifications of the CardioWave software we were able to do simulations of propagation of the action potential in a tissue level model consisting of about a 100 realistically shaped cells. The results show that the model is generating realistic propagation velocities of the action potential, and were able to explain why at the onset of ischemia we do not see any increase in this velocity due to a rise in extracellular potassium and how a reduction in extracellular space is counter acting the effects of the rise of extracellular potassium in terms of propagation velocities of the action potential.

Computation of electric field in torso of a child (Collaborator Dr. Treidman)

In this project Drs. Triedman and Jolley have segmented an entire torso model. This segmentation provided both a useful prototype dataset, as well as useful experience for identifying shortcomings in the existing tools. Dr. Jolley visited the Center for Integrative Biomedical Computation to participate in our Workshop in April, and this provided an excellent opportunity for synchronizing our efforts on this project. We have written a first manuscript based on this collaborative project, which we recently submitted for publication to the IEEE EMBS Conference.

CT Imaging of blood vessel in transgenic mouse models for human tumors (Collaborator Dr. Keller)

In this project we have done initial studies involving the practical considerations for visualizing the vascular network of transgenic mouse tumors. We have also coauthored a manuscript that was published as the cover story of PLoS genetics on using visualization and segmentation for virtual histology of mouse embryo datasets for embryo toxicity studies (J.T. Johnson et al., "Virtual Histology of Transgenic Mouse Embryos for High-Throughput Phenotyping", PLoS Genetics, 2, pp. 471-477, 2006.).

Microscopy image analysis and visualization (Collaborator Dr. Ellisman)

For this project we are currently implementing a segmentation application called BioPainter. Progress has been made on the construction of this application and we will be soon testing it for segmentation.

Mouse skeleton phenotyping (Collaborator Dr. Capecchi)

For this project, technicians at the Capecchi lab have produced a total of 20 CT image datasets, including 12 wild-type mouse scans and 6 homozygous mutant mouse scans. We are currently producing results for the first of the two research papers outlined in the preceding section. We have a set of wild-type mouse bone

segmentations and are performing the mutant segmentations as we receive new data sets. Our preliminary results suggest that we will be able to reproduce the major results of Boulet and Capecchi. These segmentations are also a prerequisite for the shape analysis work. For the latter study, we implemented our entire shape analysis pipeline and are currently testing it on various medical image data sets, including the wild-type mouse bone segmentations.