Biomedical Visual Computing: Case Studies and Challenges

Advances in computational geometric modeling, imaging, and simulation let researchers build and test models of increasing complexity, generating unprecedented amounts of data. As recent research in biomedical applications illustrates, visualization will be critical in making this vast amount of data usable; it's also fundamental to understanding models of complex phenomena.

Computer simulation and visualization are having a substantial impact on biomedicine and other areas of science and engineering. Advanced simulation and data acquisition techniques allow biomedical researchers to investigate increasingly sophisticated biological function and structure. A continuing trend in all computational science and engineering applications is the increasing size of resulting datasets. This trend is also evident in data acquisition, especially in image acquisition in biology and medical image databases.

For example, in a collaboration between neuroscientist Robert Marc and our research team at the University of Utah's Scientific Computing and Imaging (SCI) Institute (www.sci.utah.edu), we're creating datasets of brain electron microscopy (EM) mosaics that are 16 terabytes in size.[1] However, while there's no foreseeable end to the increase in our ability to produce simulation data or record observational data, our ability to use this data in meaningful ways is inhibited by current data analysis capabilities, which already lag far behind. Indeed, as the *NIH-NSF Visualization Research Challenges* report notes, to effectively understand and make use of the vast amounts of data researchers are producing is one of the greatest scientific challenges of the 21st century.[2]

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Visual data analysis involves creating images that convey salient information about underlying data and processes, enabling the detection and validation of expected results while leading to unexpected discoveries in science. This allows for the validation of new theoretical models, provides comparison between models and datasets, enables quantitative and qualitative querying, improves interpretation of data, and facilitates decision making. Scientists can use visual data analysis systems to explore "what if" scenarios, define hypotheses, and examine data under multiple perspectives and assumptions. In addition, they can identify connections between numerous attributes and quantitatively assess the reliability of hypotheses. In essence, visual data analysis is an integral part of scientific problem solving and discovery.[3]

As applied to biomedical systems, visualization plays a crucial role in our ability to comprehend large and complex data—data that, in two, three, or more dimensions, convey insight into many diverse biomedical applications, including understanding neural connectivity within the brain, interpreting bioelectric currents within the heart, characterizing white-matter tracts by diffusion tensor imaging, and understanding morphology differences among different genetic mice phenotypes.

Biomedical Case Studies

Biomedical researchers have diverse needs in relation to visual data analysis. Here, I highlight

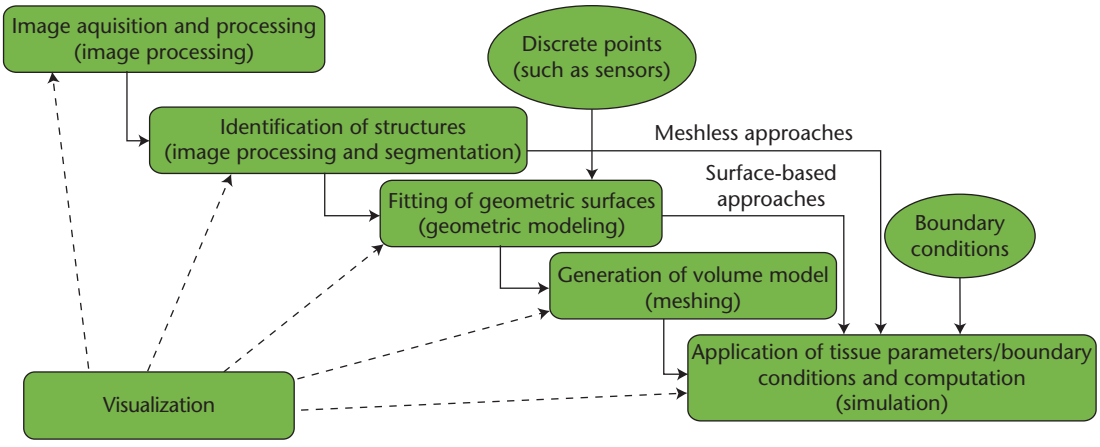


Figure 1. Biomedical image-based modeling, simulation, and visualization pipeline. Once created, the pipeline can be used in many different biomedical or other science and engineering fields.

some of those needs by discussing three ongoing collaborations among biomedical researchers and computational scientists.

Case Study 1: Simulation of Implantable Cardiac Defibrillators

Many biomedical simulation studies are based on a similar sequence: researchers begin with an image, create a geometric model, assign tissue and other material properties, run a numerical simulation, and finally visualize the results. Because the images—often sets of images that combine to describe volumes—come from many modalities, the task then becomes to identify structures of interest and describe those structures in a form suitable for numerically solving equations that describe the structures' function. Given the sequence's similarity across different kinds of studies, it's possible to define a pipeline for image-based model generation, simulation, and visualization—such as the one in Figure 1—that, once created, can be useful in many different biomedical or other science and engineering fields.

The above pipeline was developed specifically for the patient-specific simulation of defibrillation fields from implantable cardiac defibrillators (ICDs), starting from computerized axial tomography (CT) scan or magnetic resonance imaging (MRI) volumes and creating 3D meshes of the entire torso with heterogeneous mesh density to achieve acceptable computation times.[4,5]

This first case study's goal was to calculate the electric potentials in the body, and especially in the fibrillating heart, that arise during a shock from an ICD, more than 90,000 of which are implanted annually in the US alone. Of special interest was the use of such devices in children, who are much smaller than adults and almost always have some form of anatomical abnormality in the heart that makes patient-specific modeling essential.

To solve this problem, our SCI team collaborated with John Triedman and Matt Jolley from Harvard and Boston Children's Hospital to develop an image-based biomedical computing pipeline that would address multiple needs. Starting from patient images, researchers must first segment the images into regions of interest for the simulation, including torso, muscle, fat, lungs, ribs, and heart. To address this need, we created Seg3D, a lightweight, open source segmentation tool (see www.seg3d.org). Seg3D reads stacks of images as a volume using standard file formats and provides a set of tools to identify different regions within the image volume, thus generating a "label map" of the volume. BioMesh3D, an open source 3D-mesh-generation program (see www.biomesh3d.org), then uses this label map to create a tetrahedral or hexahedral volume mesh. Finite-element simulations of the electric fields are created using the SCIRun scientific computing problem-solving environment (www.scirun.org). We use visualization throughout the pipeline: for understanding and interacting with the segmentation data, viewing and visually assessing the 3D geometric mesh, and visually analyzing the potentially large-scale, simulation results using ImageVis3D (see www.imagevis3d.org) and visualization modules within SCIRun.

Although this first biomedical computing pipeline is challenging, to be useful for our collaborator's clinical applications, there's a second, iterative design and test pipeline that must work in an intuitive and interactive way. This second

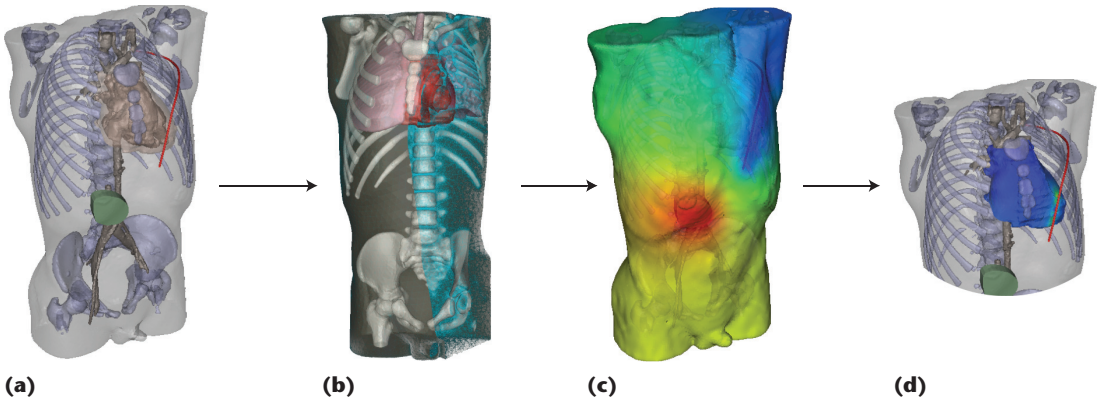


Figure 2. Pipeline for computing defibrillation potentials in children. The following are the steps required to place electrodes and compute and visualize the resulting cardiac electric potentials: (a) setting electrode configuration, (b) refinement of hexahedral mesh for electrode locations, (c) finite-element solution of electric potentials, and (d) analysis of potentials at the heart to predict defibrillation effectiveness.

modeling and simulation pipeline was executed each time the user selected a candidate set of locations for the device and the associated shock electrodes. For each such configuration, the system generated a customized version of the volume mesh and prepared it for computation.

Figure 2 shows the steps required to implement the customized mesh for each new set of device and electrode locations. As Figure 2a shows, SCIRun's interactive visual interface was important in enabling the flexible design and device component placement. BioMesh3D then carried out a refinement of the underlying 3D mesh, so that the electric potentials applied by the device and electrodes were transferred with suitable spatial fidelity to the torso volume conductor (see Figure 2b).

Simulation modules within SCIRun then computed the resulting electric field throughout the heart and torso. Next, the system visually analyzed the results, visualizing the details of the electric potentials at the heart and deriving from the simulations a defibrillation threshold value (see Figures 2c and 2d). An important aspect of this collaboration was validation of the biomedical computing pipelines with experimental results. We carried out initial validation of the complete system by comparing computed with measured defibrillation thresholds and obtained encouraging results.[5]

This case study's visualization challenges involved creating interactive, visual design, and analysis tools for large-scale complex geometries for use by our clinical collaborators. To develop effective visualization tools, we engaged in considerable discussion, interaction, and iteration with our collaborators. Creating the modeling, simulation, and visualization tools, getting them to work effectively and efficiently, and validating them on real clinical applications took several years.

This case study is one example of using simulation and visualization in a patient-specific way—an approach also known as *personalized medicine*. However, before this type of biomedical simulation and visualization can occur in a routine clinical environment, many outstanding challenges must be addressed. Generally, going from patient images to simulation results takes too long. Specifically, the image segmentation still involves significant human interaction and guidance, and the mesh generation and simulation processes for large-scale models is computationally demanding. Regarding visualization, interaction is crucial for effectively designing and testing the defibrillation electrode placement and continues to be challenging as the models become more detailed and thus larger in scale. One key visualization component missing in the current system is a visual representation of errors and simulation result uncertainties.

Case Study 2: Neural Circuit Reconstruction

Case study 2 illuminates the large-scale image analysis and visualization needs associated with better understanding the neural connectivity within the brain. Our collaborators for this were University of Utah neuroscientists Robert Marc and Erik Jorgensen.

Models of neural circuits are essential for studying the central nervous system. However, relatively little is known about the connectivities of neurons, and state-of-the-art models are typically not based on anatomical ground truth. Research in the reconstruction of neural circuits—the *connectome*—offers great promise for providing this anatomical ground truth.[6-8] Serial-section EM images can provide the data necessary to reconstruct large-scale neural circuits.

However, the images' complexity and vast size make human interpretation an extremely labor-intensive task. The pipeline for reconstructing neural circuits from serial-section EM includes preprocessing the images, assembling 3D volumes, segmenting individual neurons, and identifying and visualizing synapses and other structures (see Figure 3).[1]

Assembling the 3D neural image volumes is an important challenge complicated by the numerous 2D images that must first be mosaicked to form 2D sections and then be aligned in 3D to create volumes. Figure 4 shows a set of approximately 1,000 individual EM images used to form a 2D image mosaic. An individual tile, denoted by the red square, is 4,096 × 4,096 pixels in resolution (as a reference, full HD TV resolution is 1,920 × 1,080 pixels). A 2D image mosaic is approximately 130,000 pixels in diameter. In creating the 2D mosaics and 3D volumes, we must correct nonlinear distortions due to imaging and cutting to create a seamless volume. In addition, scaling these methods to handle the large volumes produced by our collaborators is computationally expensive. We developed open source multithreaded algorithms to solve this image-alignment problem for connectomics and to visualize the resulting neuronal volume.[1,12]

To visualize the 2D image mosaics and full 16.5-Tbyte 3D image volumes, we used ImageVis3D and visualization streams for ultimate scalability using ViSUS,[13] which uses a hierarchical, space-filling curved data structure to intelligently reorganize the raw data, enabling efficient, streaming pipelines that process the information while in motion. The results are then visualized in a progressive environment allowing for meaningful explorations with minimal required resources.

As Figure 5 shows, ViSUS enables real-time management and visualization of very large datasets such as the 3D neural image volumes. In this collaboration, I'm reminded of Anton Leeuwenhoek, one of the innovators of the light microscope, who noted that he could make new scientific discoveries "by looking," because his latest microscope let him see what others could not. The combination of the EM microscope technology created by Robert Marc's neuroscience laboratory and the new data management and visualization algorithms and software we created have allowed neuroscience researchers to visually analyze their data in new ways and to see neural images at resolutions they haven't been able to previously visualize.

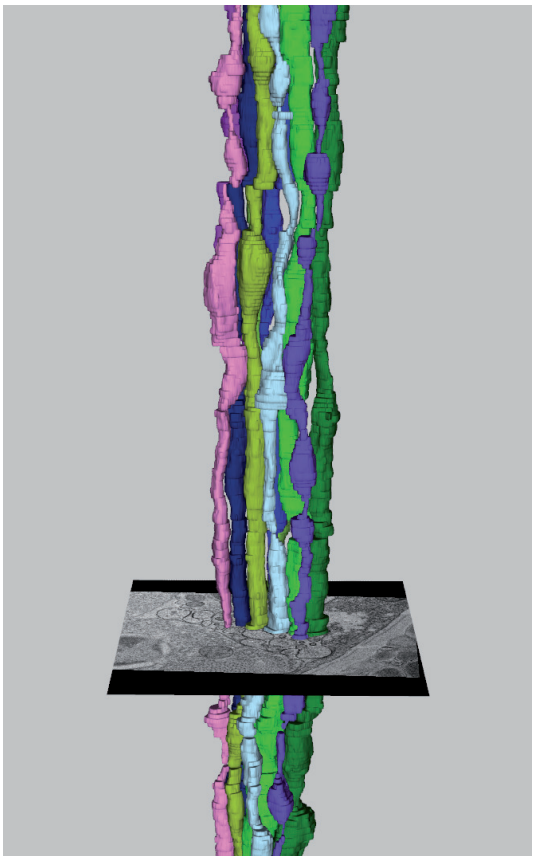


Figure 3. A view of 10 neurons spanning 300 sections of the Caenorhabditis elegans worm's ventral nerve cord. Neuron membranes were automatically detected in each 2D electron microscopy,[9] and regions between each image were joined using an optimal path-finding algorithm.[10] To make these images, neuron paths were generated automatically between six pairs of sections containing known breaks in the image data. We used our neuron reconstruction viewer (NeRV)[11] to connect paths between the breaks and correct segmentations. These visualizations reveal the complex and changing cellular structure of neurons as they move within the ventral nerve.

The visualization and image analysis challenges for this second case study are myriad. Interactive large-scale visualization is needed at each step of the connectomics construction and analysis pipeline: mosaic data, registering mosaicked data, visualizing a large volume of image mosaics, annotating those data, and visualizing annotated or derivative operations to examine connectivities or domains associated with annotation. Currently, with the state-of-the-art algorithms and software, it takes several hours to segment and annotate connectomics datasets. Although it might not be possible to fully automate the process, significantly decreasing the time it takes for segmentation and annotation is an ongoing challenge.

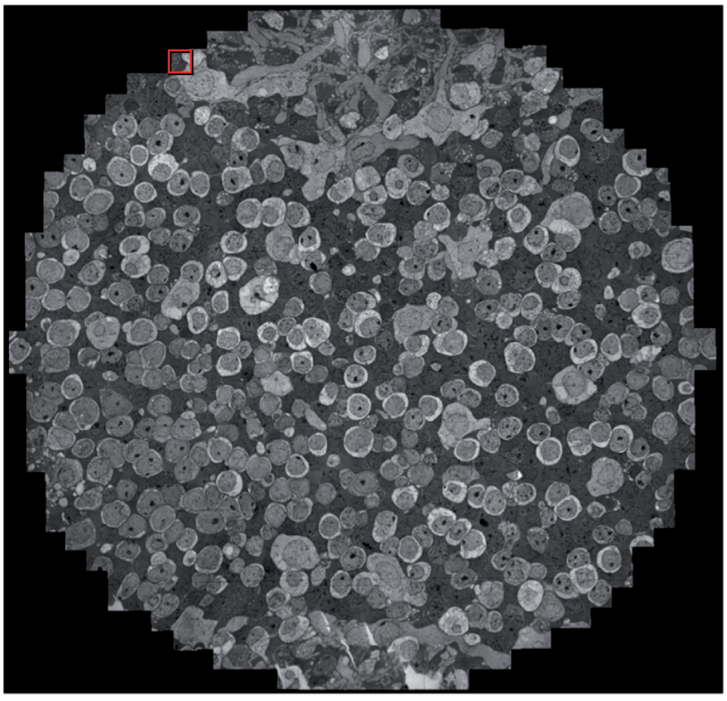


Figure 4. One section from the 342-section 3D electron microscopy retina connectome dataset. Each section is a mosaic of approximately 1,000 image tiles that are each 4,096 × 4,096 pixels. The inplane resolution is 2.18 pixels per nanometer and the section thickness is 90 nm. The full 3D connectome dataset is 16.5 terabytes.[1]

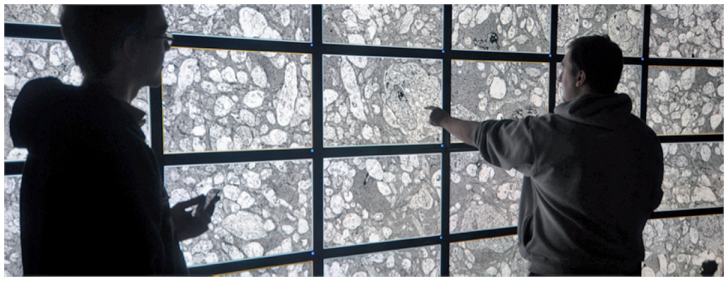


Figure 5. Visualization of the retina connectome dataset on a Powerwall with 24 30-inch monitors. The Visualization Streams for Ultimate Scalability (ViSUS) software system enables real-time management and visualization of very large datasets, such as 3D neural image volumes.

Visually characterizing segmentation and annotation errors could enable rapid revision of connectivities. Although the connectomics datasets are already large (16 Tbytes), they continue to grow. Perhaps more important will be the number of datasets. As the technology to image, segment, and annotate connectomics datasets gets better, it will take less time to create more data, perhaps following a trajectory similar to that of genetics.

As more connectomics datasets are created, many new challenges arise in comparing datasets: How many cells of a particular type exist between wild-type and genetic mutant? How is the wiring different between genetic variations? After cells are damaged, when and how does rewiring occur? Can we extract the structure of a particular cell or region to perform functional simulation? The answers to all of these questions require elements of visual analysis.

Case Study 3: Medical Visualization on Mobile Platforms

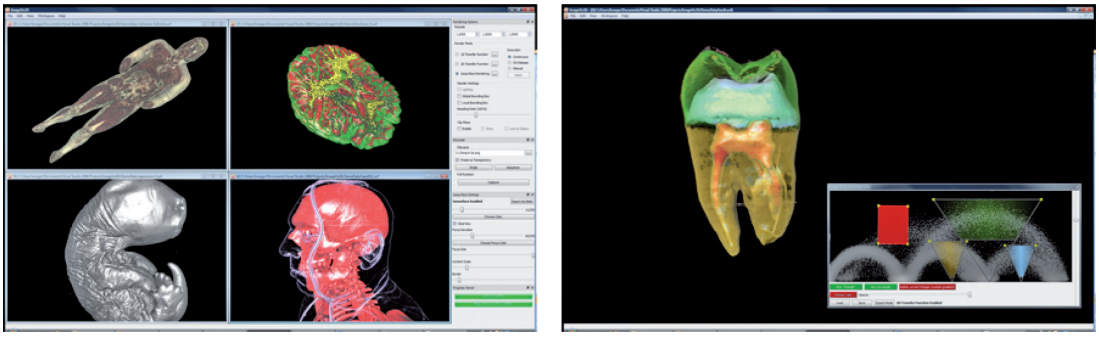
In medicine as elsewhere, there's an increasing need for visual analysis capabilities on smart phones, tablet computers, and netbooks. With their small size and less powerful processing capabilities, client–server and data streaming technologies play an important role in allowing interactive visualization on mobile computing platforms. In case study 3, we collaborated with Chris Butson of the Medical College of Wisconsin's Department of Neurology to present results from a deep-brain stimulation (DBS) visualization application used in neurology.[14]

In recent years, researchers have increasingly used patient-specific models to predict the effects of neuromodulation therapies such as DBS.[15–17] However, translating these models from a research environment to the everyday clinical workflow has been a challenge, primarily because of the models' complexity and the specialized software required to provide the visualization.

In this case study, we describe the use of ImageVis3D Mobile in an evaluation environment. ImageVis3D Mobile was designed for mobile computing devices such as the iPhone or iPad; we used it to visualize models of four Parkinson's patients who received DBS therapy. Selecting DBS settings is a significant clinical challenge that often requires repeated revisions to achieve optimal therapeutic response, and it's often performed without the advantage of the stimulation system's visual representation in the patient. We used ImageVis3D Mobile to provide models to movement-disorder clinicians and asked them to use the software to determine

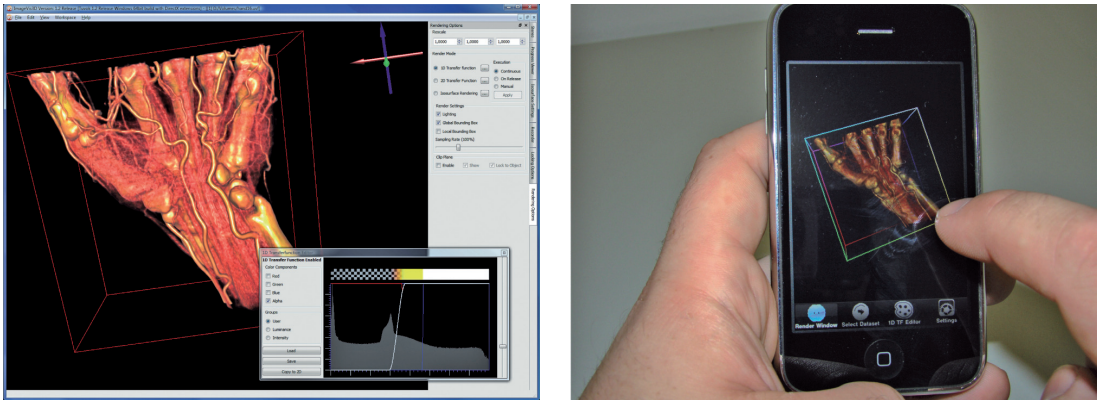
- which of the four electrode contacts they would select for therapy, and
- which stimulation settings they would choose.

ImageVis3D (shown in Figure 6) is an open source, cross-platform volume visualization program that scales to very large data on modest hardware. The main design goals of ImageVis3D are simplicity, scalability, and interactivity. Simplicity is achieved with a new user interface that gives an increased level of flexibility. Scalability and interactivity for



(a) (b)

Figure 6. Two screenshots of the ImageVis3D volume-rendering application. In the left image, four large biomedical datasets have been loaded simultaneously, accounting for approximately 50 Gbytes of data. In the right image, another dataset is loaded into the same program. As you can see, the user interface is flexible and easy to reconfigure.



(a) (b)

Figure 7. ImageVis3D and ImageVis3D Mobile visualizing the same x-ray computed tomography (CT) dataset of a hand. The mobile visualization capabilities make it possible to constantly monitor time-critical simulations and experiments and view, share, and discuss datasets in the field.

ImageVis3D mean that the user can interactively explore very large (gigabyte and terabyte) datasets on either a notebook computer or a high-end graphics workstation. ImageVis3D's open source nature and strict component-by-component design lets developers not only extend ImageVis3D itself, but also to reuse parts of it—such as the volume-rendering core—for other visualization applications.

Because some of ImageVis3D's volume-rendering techniques[18] support all major PC operating systems (Windows, OS X, Linux) and a wide range of graphics hardware, it can be run on tablets, notebooks, netbooks, and other portable devices. Such handheld devices are advantageous in that they're always available without the need to carry additional hardware. With mobile visualization capabilities, it's possible to constantly monitor time-critical simulations and experiments and to view, share, and discuss datasets in the field, where they're most relevant. To suit these needs, we recently developed ImageVis3D Mobile (see Figure 7).

To implement ImageVis3D Mobile, we chose Apple's iPhone and iPad OS software platform for two reasons. First, the iPhone OS runs on every iPhone, iPod touch, and iPad and has a large base of existing devices in the field. Second, it builds on industry standards such as OpenGL ES, making ImageVis3D Mobile easily ported to other devices. Finally, the hardware design, such as the amount of memory, the CPU, and the GPU used on the iPhone and iPad, reflects the design of many other current and upcoming mobile devices.

Figure 8 illustrates a DBS system and shows a patient-specific visualization of DBS that provides the location of the electrode lead relative to the surrounding nuclei in a Parkinson's disease patient.

We compared the stimulation protocol chosen from the software with the stimulation protocol that was chosen through clinical practice, independent of the study. We then compared the amount of time required to reach these settings using the software versus standard practice.

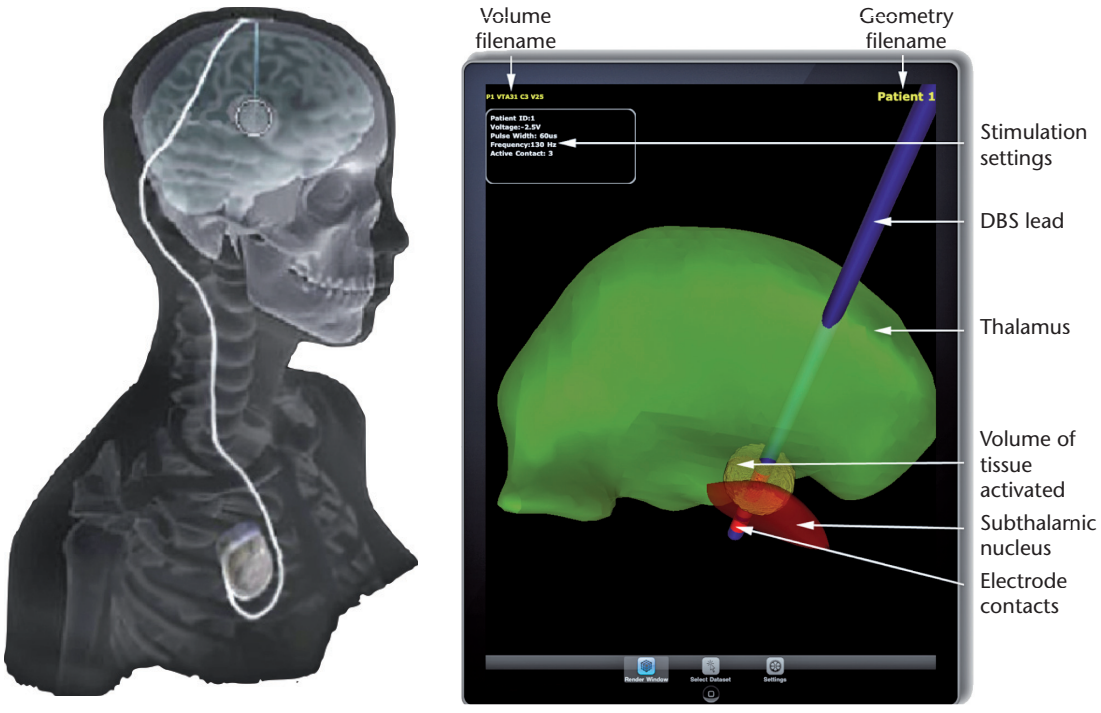


Figure 8. A deep-brain stimulation (DBS) system and model. (a) System overview. The DBS electrode is implanted in the brain during stereotactic surgery. The electrode is attached via an extension wire to the Inter Pixel Gap (IPG), which is implanted in the torso. The entire system is subcutaneous and designed to deliver continuous stimulation for several years at a time. (b) A patient-specific DBS model shows the location of the electrode lead relative to the surrounding nuclei in a Parkinson's disease patient. A model-predicted volume of tissue activated (VTA) during DBS (the yellow section) is shown surrounding the distal electrode contact. With this model, it's possible to view the overlap between the VTA and nearby anatomical structures, which is a key feature in clinical decision making when choosing stimulation settings.

We found that the stimulation settings chosen using ImageVis3D Mobile were similar to those used in standard care, but were selected in much less time. ImageVis3D Mobile is an example of how a visualization system—available directly at the point of care on a device familiar to the neurologist—can improve critical clinical decision making.[14]

The visualization challenges for case study 3 involve creating effective visualization systems and interfaces on mobile devices such as the iPhone and iPad. The technical issues involve creating interactive visualization algorithms that could either run on the mobile device or use a client–server renderer. The user interface had to be custom designed to the clinical application and tested with neurologists.

Current DBS systems have mainly used programming devices that provide no visualization at all. It's up to the clinician to integrate the patients' responses to DBS, along with knowledge of the anatomy and make meaningful decisions on how to choose stimulation settings. From our work with physicians, there's a clear desire for visualization during programming, and the use of interactive visualization can improve the efficiency of DBS programming. The challenge will be designing a set of visual analysis tools that will lead to the most improved patient outcomes.

Biomedical Visual Computing Challenges

New imaging modalities, more accurate simulation models, and continued growth in computational power all contribute to confronting biomedical researchers and engineers with an unprecedented volume of information to further their understanding of biological systems and improve clinical practice. As the size and complexity of the resulting data explode, the tools created by visualization research become crucial for gaining insight into the underlying biophysical phenomena.[19]

There's a common assumption that with more data comes more insight; that the current exponential increase in data somehow equals an exponential increase in understanding; and, that if we just

accumulate enough data, long-standing scientific problems will be solved. Unfortunately, the amount of insight and understanding aren't directly proportional to the amount of data created. Our current data and visual analysis capabilities lag far behind our ability to produce simulation data or record observational data. We're data rich, but analysis poor.

Fundamental advances must be made to extract meaning from large and complex datasets derived from experiments and from ever-growing simulation systems. As these three case studies show, such advances require close cooperation with the biomedical researchers and clinicians. Solutions often involve

- creating effective new visual abstractions;
- advancing scalability through new algorithm development;
- designing intuitive, easy-to-use interfaces; and
- modifying existing software and creating a significant amount of new software.

Effective data analysis and visualization tools in support of predictive simulations and scientific knowledge discovery must be based on strong algorithmic and mathematical foundations that allow scientists to reliably characterize salient features in their data. To accomplish this, we'll need to provide new capabilities for verification and validation of simulation and visualization codes. While the simulation community is making significant progress in this regard,[20] the visualization community has just started to consider these issues.[21]

In relation to verification and validation, we must provide scientists with uncertainty representation and quantification, uncertainty propagation, and uncertainty visualization techniques so that they can better understand the limits of their simulations and visualizations.[22] Visual representations of error and uncertainty were missing from all three case studies. This area represents an important ongoing visualization research challenge.[23]

Although the case studies presented here were diverse, there are many other exciting biomedical visualization examples, including information visualization applications in genetics,[24] epidemiology,[25] and other biological applications.[26]

To help researchers gain insight into their ever-growing and complex data, we must develop new approaches to visual data analysis and knowledge discovery. Such approaches must

- account for the often multilevel nature of data;
- let scientists easily transition views from global to local model data;
- offer the ability to blend traditional scientific and information visualization;
- perform "what if" scenarios, uncertainty analysis and verification, and validation; and
- address the challenges posed by vastly different geometric models used by the various elements of the multilevel projects.

Interacting with biomedical scientists and clinicians is critical for developing useful software tools. Tools that leverage semantic information and hide details of dataset formats will be important in letting visualization and analysis experts concentrate on designing their approaches rather than becoming mired in the trivialities of particular data representations; they will also help in designing effective user interfaces.[3]

There are many other exciting biomedical visualization examples, including information visualization applications in genetics, epidemiology, and other biological applications.

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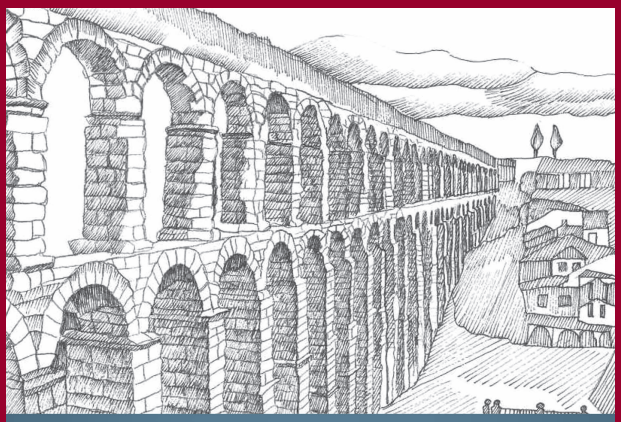

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