Biomedical Imaging: Past, Present and Predictions

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ABSTRACT

Biomedical imaging has a long history, dating back several centuries if one considers the study of anatomy via cadaveric dissection and exploration in medieval autopsy theaters. However, the era of modern medical imaging, where real images were made of the internal body and its contents without dissection, began in the late 1800's with the discovery of x-rays by Roentgen. Although improvement in recording media considerably enhanced the quality and use of x-rays for medical purposes, with the notable exception of fluoroscopy and nuclear imaging developed decades later, it was not until the early 1970s that a new revolution began in medical imaging, namely computed tomography, and imaging capabilities since that time have been developed, applied and accepted at a volume and pace that is unprecedented in medical history. By comparison to those extant even 30 or 40 years ago, current capabilities are truly remarkable and have clearly established an expectation for continuing advances that will be just as outstanding in the next few years and beyond. This paper attempts to briefly summarize the history of visualizing the internal body for medical and biological purposes, with primary focus on present capabilities. A few predictions will be made by extrapolating from present to possible future advances. Copious citations will not be used, as most of this treatise is based on 3 decades of personal opinion and experience, but a few references to personal publications are attached that contain numerous citations to the topics included in this perspective – past, present and future [1-10].

1. INTRODUCTION

The practice of medicine and study of biology have always relied on visualization to study the relationship of anatomic structure to biologic function and to detect and treat disease and trauma that disturb or threaten normal life processes. Traditionally, these visualizations have been either direct, via surgery or biopsy, or indirect, requiring extensive mental reconstruction. The revolutionary capabilities of new three-dimensional (3D) and four-dimensional (4D) medical-imaging modalities [computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound (US), etc.] along with computer reconstruction and rendering of multidimensional medical and histologic volume image data, obviate the need for physical dissection or abstract assembly of anatomy, and provide powerful new opportunities for medical diagnosis and treatment, as well as for biological investigations. Locked within 3D biomedical images is significant information about the objects and their properties from which the images are derived. Efforts to unlock this information to reveal answers to the mysteries of form and function are couched in the domain of image processing and visualization.

Visualizable objects in medicine extend across a vast range of scale, from individual molecules and cells, through the varieties of tissue and interstitial interfaces, to complete organs, organ systems and body parts, and these objects include functional attributes of these systems, such as biophysical, biomechanical and physiological properties. Medical applications include accurate anatomy and function mapping, enhanced diagnosis and accurate treatment planning and rehearsal. However, the greatest potential for revolutionary innovation in the practice of medicine lies in direct, fully immersive, real-time multisensory fusion of real and virtual information data streams into an online, real-time visualization during an actual clinical procedure. Such capabilities are not yet available to the general practitioner. However, current advanced computer image-processing research has recently facilitated major progress toward fully interactive 3D visualization and realistic simulation. The continuing goals for development and acceptance of important visualization display technology are: (a) improvement in speed, quality and dimensionality of the display and (b) improved access to the data represented in the display through interactive, intuitive manipulation and measurement of the data represented by the display. Included in these objectives is determination of the quantitative information about the properties of anatomic tissues and their functions that relate to and are affected by disease. With these advances in hand, the delivery of several important clinical applications will soon be possible that will have a significant impact on medicine and study of biology.

If we focus on the historical evolution of medical imaging alone, leaving aside for now the significant parallel advances in biological imaging facilitated by the invention of the microscope, the field dates back to the early parts of the 12th and 13th centuries with direct visualization by dissection in anatomy theaters. This was the principal form of imaging, that is direct visualization via dissection, for almost 600 years until near the end of the 19th Century when a form of imaging was introduced to aid visualization into the body without dissection – namely the discovery of the x-ray. But, although the sensitivity and quality of recordings by this technique improved over the next several decades, and with the notable exceptions of fluoroscopy in the 1940s and nuclear imaging in the 1950s, the era of modern medical imaging did not begin until the 1970s. This modern era was heralded again by an x-ray imaging device called the "CAT" scanner or Computerized Axial Tomograph device, which has long since been called simply Computed Tomography, or CT. Soon after the advent of this scanner in the 1970s, 3D imaging became available and other modalities began to be rapidly developed. Particular note is given to magnetic resonance imaging (MRI) in the early 1980s because of its near revolutionary impact on soft tissue imaging. Nuclear systems (notably PET and SPECT) introduced functional imaging, followed by high-speed CT (helical) and rapid MR imaging (fMRI). By the decade of the 1990s, with significant performance gains in imaging methodologies, interactive multi-dimensional, multi-modality imaging for improved diagnosis, treatment, guidance and therapy monitoring became routine in large medical centers. The turn to the 21st Century was characterized by the advent of many image-guided interventions, often associated with minimally invasive surgery, for planning, rehearsal and execution of a wide variety of clinical and surgical procedures.

These significant advances have set the stage for an exciting future that will include highly sensitive and specific molecular and biochemical imaging, real-time and multi-dimensional imaging, whereby almost any number of multiple orthogonal image variables can be fused and synchronized together to bring all collected information synergistically to bear on diagnosis and treatment of disease. The near future will demonstrate highly integrated capabilities for structural and functional information synchronously across space and time, and this will drive the practice of medicine of the future toward truly synchronous, minimally invasive, highly specific, highly sensitive and highly effective diagnosis and treatment of disease.

2. THE EVOLUTIONARY PAST

Medical imaging may be considered to have started in medieval times with illustrated art depicting the direct visualization of internal body anatomy during dissection of cadavers, as illustrated in Figure 1. Even though this seems primitive to us today, one should not readily dismiss the value of these early "physicians" in visualizing the corporeal body, the relative position, size and shape of organs, and the potential nature of function to anatomy relationships that could be observed from these early visual explorations into the dissected body.

Figure 1. Illustrations of medieval anatomy theaters featuring cadaveric dissection for visually "imaging" internal organs.

But perhaps the true start of medical imaging as we consider it today was in 1895 when Roentgen discovered the x-ray. This marvelous discovery was rapidly developed into imaging techniques for medical purposes. For example chest radiography became one of those early applications, even though the equipment seems crude by comparison to that of today, and certainly there was no knowledge of the potential deleterious effects of the ionizing radiation of x-rays. Figure 2 illustrates the invention of Roentgen and (arguably) the first x-ray of human anatomy (note the ring on the finger).

From: O. Glasser, Wilhelm Conrad Röntgen And The Early History Of The Roentgen Rays, Thomas Books 1934, p. 25

Figure 2. Wilhelm Conrad Roentgen and early x-ray of his wife's hand, heralding the start of the modern era of medical imaging.

In the decades following, several applications demonstrated for the first time the ability to look inside the body without dissection to study internal anatomy. Over the years there have been, of course, significant improvements in the x-ray technique, primarily due to the higher sensitivity and fidelity of the recording films, not necessarily any significant advances in the basic methodology.

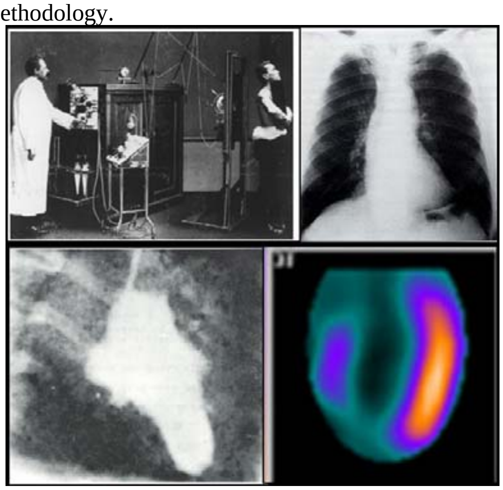

Figure 3. Primitive chest x-ray system and examples of x-ray, fluoroscopy and nuclear imaging.

Figure 3 shows an early chest x-ray system and chest radiograph along with an image of a fluoroscopic view of the heart with radio-opaque contrast material in a chamber, and a nuclear image of the heart walls with a radioisotope injected. Such images have been used for more than 50 years to make critical diagnoses and discoveries of diseases that occur in the chest and heart. It wasn't until 1970 with the announcement of the x-ray CT scanner that a major new advance took place in medical imaging. This device contributed three major significant features to medical imaging that continues to be its foundation today: 1) the image was digital, produced by a computer, and could be readily modified, analyzed and displayed by computers, 2) the method provided sensitivity to tissue density differences unattainable theretofore, and 3) the methodology provided cross-sectional views of the human body, eventually multiple cross-sectional views adjacent one to another, providing a three dimensional view of internal anatomic structures. Since the body is 3D and the organs have different shapes, sizes and positions relative one to another in 3D space, imaging adjacent thin body cross sections was an important advance in medicine's ability to more accurately see and understand the true nature of objects inside the body.

Figure 4 shows Nobel laureate Godfrey Hounsfield with an early CT head scanner he invented and a very early example of a cross section of the brain. This image, crude by today's standards, nonetheless generated great excitement in the radiologic and medical community with the ability to see small differences between tissue opacities in a cross-section of the brain. As the CT technique improved and increased spatial resolution and contrast sensitivity, remarkable images of the internal brain began to be realized, including clear separation of white and gray matter. MR imaging followed in the 1980s, based on the mathematical image reconstruction techniques, but featured much higher resolution of soft tissue differences than x-ray CT. Also shown in Figure 4 is the scale of numbers that Hounsfield developed, which quantified tissue types according to relative x-ray attenuation, ranging from air to bone. This digital scale became standardized and represented numerically the image output of the computed tomography scanner.

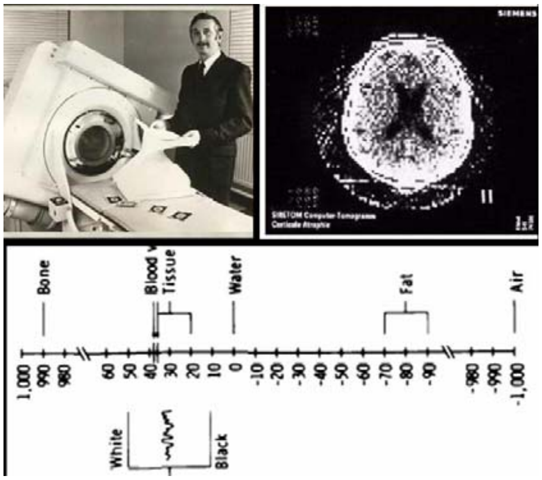

Figure 4. Godfrey Hounsfield and first "CAT" scanner developed in early 1970's and first cross sectional image of head. Hounsfield scale was developed to enumerate tissues.

The advent of computed tomography in the early 1970s inspired this author to join a multidisciplinary team at the Mayo Clinic to develop dynamic volume imaging of the cardiopulmonary system. This followed his early attempts in the mid 1960s using biplane fluoroscopic cardiac angiograms to segment and reconstruct the three dimensional beating heart throughout the cardiac cycle. The efforts of the Mayo Clinic team, lead by Dr. Earl Wood, resulted in development of the Dynamic Spatial Reconstructor (DSR) in the late 1970s, which became the first multi-source, multi-detector, real-time, 4D CT imaging system. This innovative system could scan and produce image volumes of 25 cm^3 with 1 mm isotropic spatial resolution at 30 volumes/second. Contrast material was usually injected to enhance the differentiation between blood in the chambers and coronary vessels and the heart walls, as the DSR did not have as high contrast sensitivity as conventional CT (but far superior spatial and temporal resolution). Figure 5 is an illustration of this landmark scanner and examples of the data it produced.

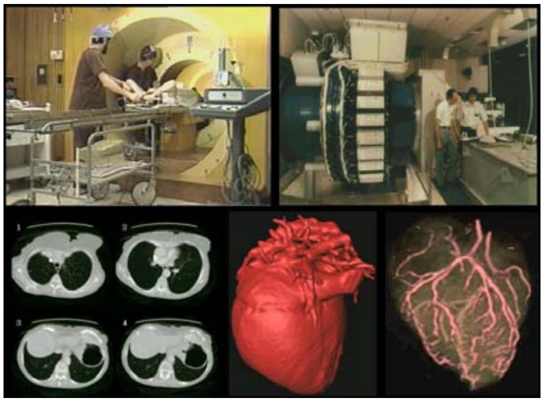

Figure 5. The Dynamic Spatial Reconstructor, developed at Mayo Clinic in the 1970's, and real-time 3D volume images of heart and coronary arteries reconstructed from DSR scans.

Over the short period of three decades, between 1970 and the turn of the century, marvelous new architectures and higher resolution, extended volume, dynamic scanning x-ray CT, MRI and nuclear (PET, SPECT) systems became available. These systems now are able to provide highly detailed three dimensional and dynamic (that is 4D) images of structure and function anywhere in the body, as is illustrated in Figures 6 and 7.

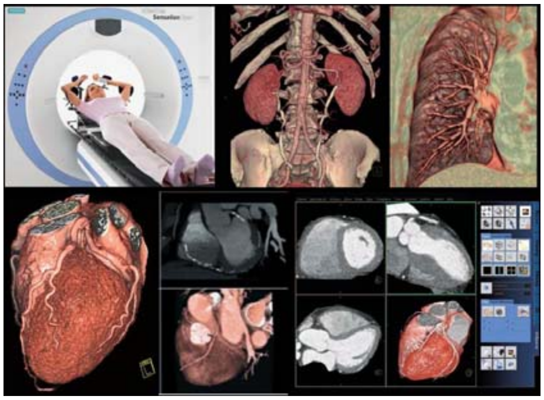

Figure 6. Modern imaging system – a 64 row helical CT scanner – and examples of 3D and 4D volume rendered images.

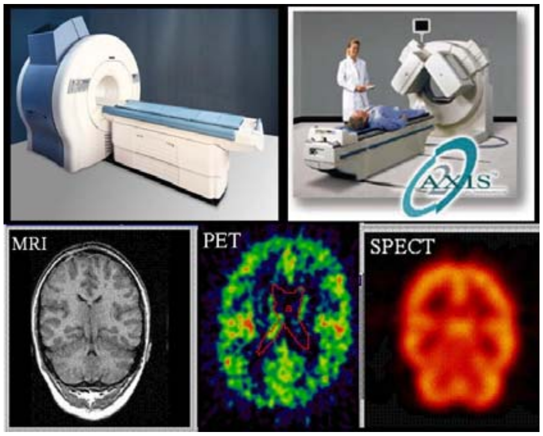

Figure 7. MRI and SPECT scanners and examples of cross-sectional images of brain obtained from them.

Current capabilities include the ability to image the beating heart and blood flow through vessels in the heart, lungs, brain, extremities, etc. Modern CT, MRI, PET, US, etc. provide complimentary differences and advantages that do not favor any one methodology alone in comprehensive medical practice. MRI systems dominated the imaging device applications in medicine throughout the late 80s and 90s because of its high resolution and sensitivity to soft tissue differences, even though longer scan times were required. With the advent of spiral or helical CT scanning, followed in more recent years by fast multiple row CT systems which provide dynamic volume scanning (inspired by the DSR), CT has rebounded as an important modality in many diagnostic and therapeutic imaging situations. PET and SPECT scanners provide functional characterization of tissue (metabolism, diffusion, etc.) and US is often performed for real-time imaging.

It would be short-sighted to not mention the important contribution of modern day computers, communication networks and associated software in the rapid evolution of modern biomedical digital imaging. Since the 1970s, microprocessor technology has advanced to provide inexpensive workstations with power that was previously the exclusive domain of supercomputers. Multiple fast processors with large amounts of resident memory and powerful graphics cards, all available at a low cost (less than $5000) and combined into a single system, have provided the impetus for development and implementation of advanced digital biomedical imaging. Software (sometimes combined with hardware) to rapidly reconstruct three dimensional volume images in real time or near real time, has made such workstations truly practical in the clinical setting. Research software packages, as well as commercial ones, have advanced the field significantly in the past three decades. The evolution of the internet and the world wide web have facilitated transfer of data, sharing of programs, publication searching and warehousing of knowledge and ideas. These have fueled the development of biomedical imaging to fever pitch, such that at present, large medical imaging meetings present the potential user and buyer of this technology an overwhelming plethora of choices, types, styles, kinds, costs and evolutionary capabilities in present day medical imaging.

3. THE REVOLUTIONARY PRESENT

Before describing and illustrating some of the medical applications of current modern medical imaging systems, it is instructive to review important first principles that underlie these capabilities. First, it should be noted that biomedical imaging is a feed-forward, feed-backward process. There are three main elements in this process: 1) acquisition of image datasets, 2) processing the image datasets, and 3) productive use of the datasets. Feedback from processing and use can help define better ways to acquire the data in order to facilitate more accurate, focused and/or expedient processing and/or to better meet the target use. This strategic imaging paradigm and its subcomponents are illustrated in Figure 8.

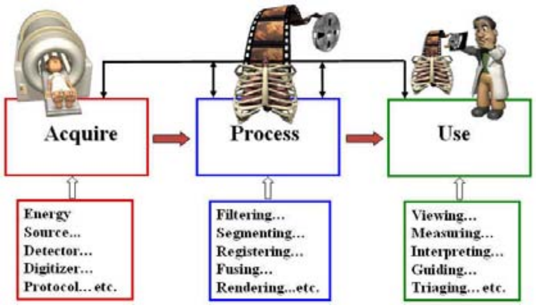

Figure 8. Flow chart of biomedical imaging process, illustrating relationships between acquisition, processing and utilization.

The three-dimensional, sometimes four-dimensional (time series) image datasets produced by modern imaging systems are generally organized into arrays of digital, numerical data. Each element in the array, called a pixel or a voxel, is fundamental to understanding image formation and composition, and to focus processing and manipulation of the data to best realize the intended use of the image. We must always remind our students in imaging science "to not forget the pixel". Table 1 is a list of some key image processing functions that are used in modern medical imaging applications. Most, if not all, of these functions are included in high performance imaging software and hardware systems. Automated accurate segmentation is the "holy grail" of image processing functions, but the associated methods of multimodality image fusion and modeling of structure-function relationships are the current "hot topics" in medical imaging science. However, incremental improvements in volume rendering, speed and quality, accuracy of multimodal registration of volume datasets, including non-linear, elastic registration, and tools for measurement and quantitative analysis of the information contained in images, are all areas of research important to advancing the capabilities of medical imaging systems needed in current clinical applications.

Table 1: Key Image Processing Functions for Current Medical Applications

- Fast volume rendering
- Automated segmentation
- Robust registration
- Quantitative measurement and analysis
- Multimodality image fusion
- Realistic modeling of anatomy/function

Figure 9 illustrates the quality of images rendered from current high resolution CT and MR scans, and also indicates the separation, both spatially and feature-wise, of multiple anatomic/functional structures which can be rendered together when accurately registered, segmented and classified.

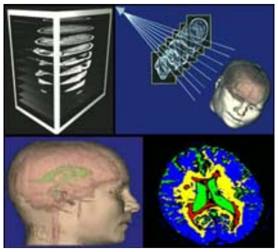

Figure 9. Example of realistic volume rendering of segmented and classified anatomic structures and tissues.

So just what is image fusion? Our definition is: *"Image fusion is the integration of multiple scalar voxel images into a single vector voxel image involving correction of any position, orientation, scaling or sampling differences among component images, thus producing a coherent image of voxel vectors potentially more useful for multidimensional image visualization, analysis and guidance than any of the constituent images alone."* Figure 10 illustrates the power of fusion of multimodality images where the fused image is comprised of vector voxels, with each voxel in the volume associated with a given number of values provided by each constituent image used in the fusion. For example, in Figure 10, if T1 and T2 MR images are available along with a CT image of the same patient, these can be registered and fused together to produce a volume of voxels where each fused image voxel is a vector of the corresponding T1, T2 and C2 image values. The rendered image can include any of these voxel elements to render a given single tissue (e.g., skull from CT), or a combination of tissues (e.g., skull and brain from CT and MR), as shown in Figure 10.

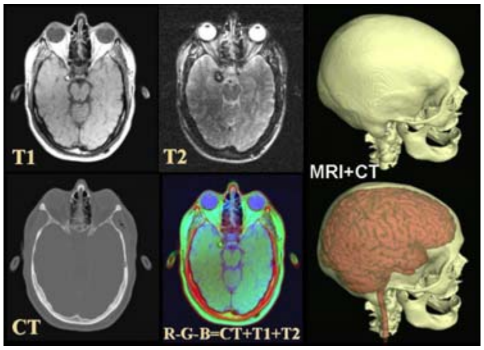

Figure 10. Left – Methodology of image fusion where multi-modality (T1, T2, CT) images are registered and synthesized into a "vector image" with multi-value voxels. Right – Rendered volume images of fused CT and MRI scans.

Fused images have great power for differentiating tissue types for signature typing of both pathology and normal tissue, and for local and focused assessment of structure-to-function relationships. Such image processing portends a significant advance in future applications of multimodality imaging in the differential diagnosis of disease and the selection of specific treatment options. Figure 11 shows combined structure and function of the brain from fused MRI and PET volume images.

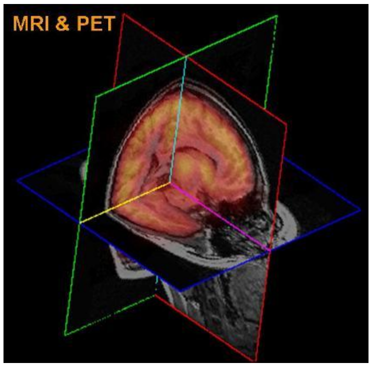

Figure 11. Example of volume image fusion of MRI and PET scans using orthogonal dissection with color-mix pixels.

Image modeling involves computing geometrically and functionally accurate representations of the body and body parts from scanned volume images. These models can be, of course, patient specific models of anatomy, physiology, pathology and more. Figure 12 illustrates the process of image modeling, proceeding from a scanned volume image represented in the numerical voxel domain, to surface models of anatomic structures represented in the geometric or polygon domain. Functional attributes, if measured synchronously and registered appropriately, can be mapped onto these modeled surfaces to add function to structure. Such functions might include regional kinetics, elasticity, electrophysiology, flow, pressure, temperature, viscosity, diffusion, stress and strain.

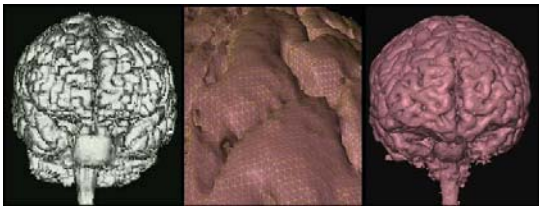

Figure 12. Procedure for producing anatomic polygonal surface model (right) from voxel-based original volume image scans (left). Center shows close-up of surface tiles.

There are two major classes of models that are used in medical simulation for training, rehearsal and guidance in interventional procedures. The first class may be referred to as simulated reality, which involves models of real objects developed from images and simulated versions of real procedures which use these models. Examples are virtual endoscopy and virtual surgery. The second class of model is used in augmented or enhanced reality applications. This involves real-time, online fusion of simulated models with real-time images and tools for use in guiding on-line interventional procedures, for robot-aided surgery, telemedicine, etc. Figure 13 is an illustration of enhanced reality used in medical applications, namely cardiopulmonary and brain surgery.

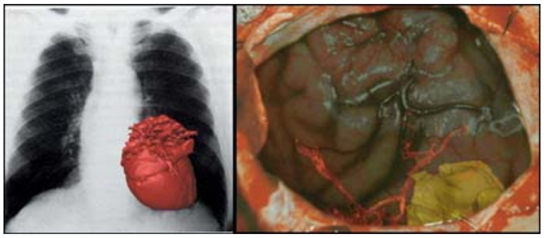

Figure 13. Enhanced reality combines computed anatomic surface models with real-time image data streams (x-ray, video) to enhance visualization and guide interventional procedures.

The overall process of patient specific anatomy and function modeling is summarized in Figure 14. From left to right, the process involves scanning the patient, segmenting the organs of interest and producing anatomic models, mapping any available desired functions onto these models, interacting with the structure-to-function model, and then using the model in a particular clinical application. From top to bottom this process can be applied at the macro level, including large body parts and anatomic organs, to the micro level, involving tissues, cells and molecules.

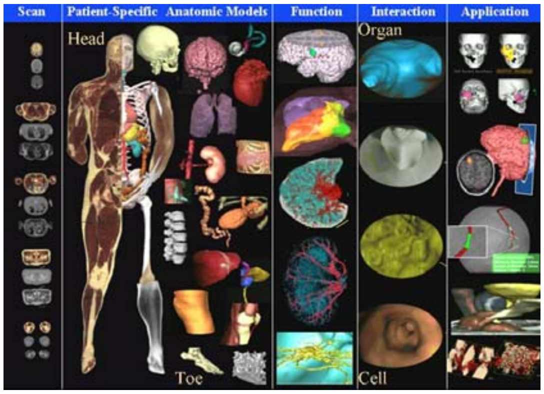

Figure 14. Patient-specific imaging, modeling and application. Left-to-right: scan data, segmentation and modeling, functional mapping, interactive display, and clinical use. Top-to-bottom: range of scale, organs to cells.

The number of clinical applications of medical imaging is large and growing. A few exemplary applications will be included here with illustrations of their clinical potential. These will include craniofacial surgery planning, neurosurgery planning, cochlear implant planning, diagnosis and treatment of heart and coronary artery disease, characterization of pulmonary disease, detection and diagnosis of colon cancer and applications in prostate cancer.

Craniofacial surgeons were early adopters of three-dimensional imaging. They began to use CT imaging of the head in the late 1970s and early 1980s, and continue to the present. Figure 15 is an illustration of the application of 3D CT images of the head segmented, rendered and manipulated on computer workstations to design a facial implant to fill a defect in a patient's skull. Such procedures are currently routine in major medical centers.

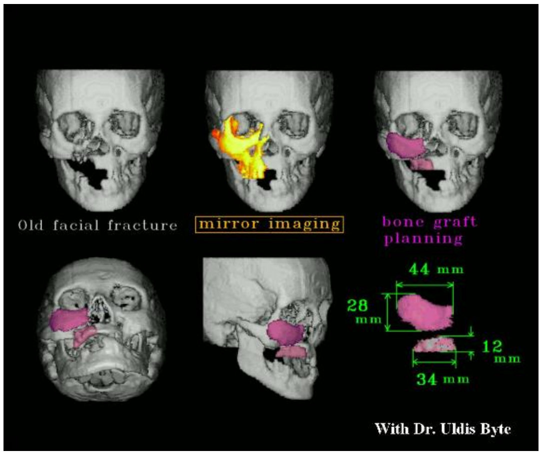

Figure 15. Craniofacial surgery planning using 3D imaging. Implant to fill facial defect is designed on a workstation.

Figure 16 shows a procedure developed by our lab at the Mayo Clinic called SISCOM, an acronym for Subtraction Interictal Spect Coregistered to MRI. In this procedure, epilepsy patients who do not respond to medication and have intractable seizures, are treated surgically by first doing two radioisotope scans, one just following a seizure (ictal stage), and one during quiet time (inter-ictal stage). These two SPECT (or PET) images are registered and subtracted to provide a difference image which highlights on the activation area in the cerebral cortex giving rise to the seizures. Since this is not an anatomically specific image, an MRI scan of the patient is also performed, and the difference SPECT image and the MRI image are registered, fused and rendered to illustrate with high spatial accuracy the cortical anatomy and specific regions of seizure activation. This guides the neurosurgeon to make a precise and accurate resection of the brain tissue to eliminate the seizure activity, while at the same time minimizing any trauma or damage to surrounding normal tissue.

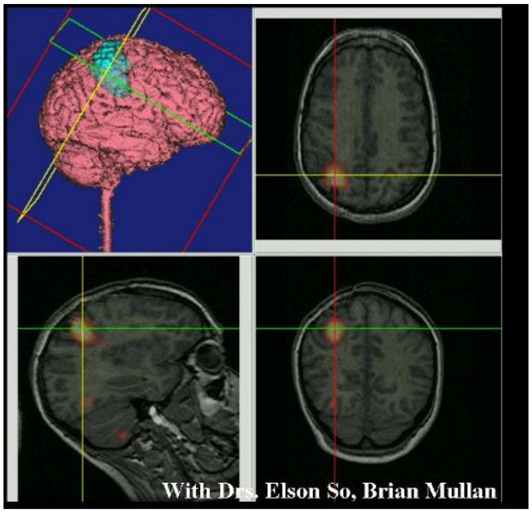

Figure 16. SISCOM technique for localizing region of seizure activation for resection in brain of epilepsy patient.

Figure 17 shows the application of 4-dimensional high resolution imaging to the diagnosis and staging of cerebral aneurysms. High-speed multi-row helical CT scans can be used to produce these remarkable images to delineate the location, size and shape of the cerebral vasculature and any developing aneurysms. In dynamic mode, the pulsatile flow through the larger blood vessels, including the aneurysm, can be observed.

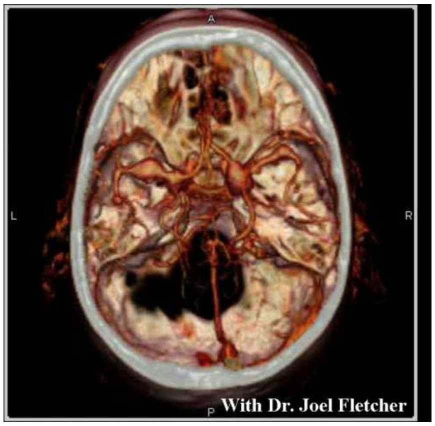

Figure 17. 4D imaging of brain aneurysm with dynamic CT.

Figure 18 shows an application of high field strength MR imaging (3 Tesla) to volume imaging of the auditory canal to help plan cochlear implants. An important decision in this process is to determine if the auditory nerve is viable, that is, if it has atrophied and therefore may not adequately conduct sound signals along its pathway to the brain. The size of this nerve can be accurately calculated from such volume image scans. The optimal surgical approach to the site can be planned, and the precise location for placing the implant determined.

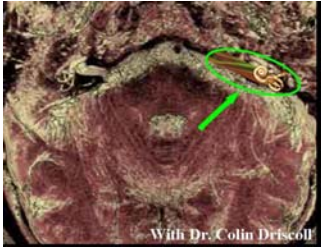

Figure 18. Image-guided planning of cochlear implant using high resolution MR images of auditory canal.

Figure 19 shows an application of multimodality imaging to diagnosis and treatment of coronary artery disease. Biplane fluoroscopic images are used to track in three dimensions catheters placed into the coronary arteries. One of these catheters can be an intravascular ultrasound (IVUS) imaging device which provides cross sectional images along the pathway of the artery. Computer processing of IVUS images using multispectral analysis can help identify individual plaques and plaque-burden along the artery, and quantitatively characterize plaque composition, e.g., hard or soft (degree of calcification). The integrity of the arterial wall, its elasticity and other biophysical properties, can also be calculated from these images. All of this data can be used to determine the most effective treatment for the coronary plaque – medication, radiation, topical chemicals or perhaps stenting. If plaques are soft, they're vulnerable to rupture from physical interventions, such as stenting. In the case of firm plaques, the tracked three dimensional images can be used by the cardiologist to precisely place a stent in the region of the plaque to effectively open the vessel and keep it patent, minimizing the possibility of re-stenosis.

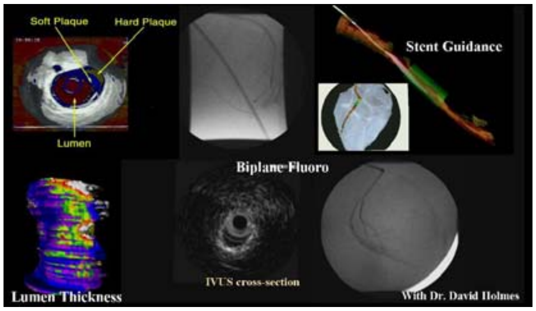

Figure 19. Fusion of bi-plane fluoro, IVUS and computed images to detect and characterize coronary artery plaques and vessel wall and to guide placement of stents.

Figure 20 shows an application which we call 5D image-guided cardiac ablation. Patients with cardiac arrhythmias can be treated by direct surgical resection of the heart muscle or by catheter-based ablation of the affected anatomic region using focused high energy beams. An image-guided procedure can provide detailed anatomy (3D), through time (4D), and mapping of real-time electrophysiology onto the beating heart walls (5D). These 5D images of the heart can be viewed from any point of orientation, inside or outside of the heart, and the progression of nerve activation signals shown as a continuous pattern of color superimposed on the moving walls of the heart chambers. The display can also be static at any selected point in the cardiac cycle. The electrophysiologist or cardiologist can view the dynamic visualizations in real time during the procedure. Using such visual guidance, the ablation catheter, which can also be seen in the field of view, can be precisely positioned to point toward the offending region of tissue as highlighted on the color map, and ablation accurately accomplished. This obviates the time-consuming "hit and miss" trial sequence routinely used in this procedure. This new 5D image guidance method will reduce the procedure time from typically 8-10 hours to 1-2 hours, with associated benefits of high positive outcomes (95%), low morbidity and reduced cost. The open heart surgical approach will become essentially obsolete.

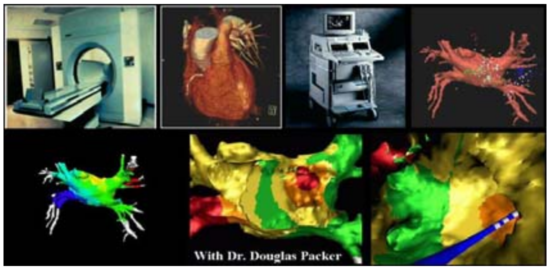

Figure 20. 5D imaging for accurate guidance of catheter-based cardiac ablation. 3D images are acquired and fused with electrophysiology mappings in real-time, highlighting for ablation the precise location in the heart of the focal arrhythmia.

Figure 21 shows the application of high resolution chest imaging in diagnosing and staging both diffuse and localized lung diseases, such as emphysema, asthma and cancer. Pathology can be accurately detected and quantified by high resolution CT chest volume scans, and conducted rapidly enough to collect these volumes throughout successive points in a respiratory cycle or at end-inspiration and end-expiration permitting analyses of the mechanics of the pulmonary parenchyma through the respiratory cycle. Such dynamics can be color mapped onto the lung surfaces to directly provide a quantitative impression of the location and severity of the disease, and evaluation of both regional and global response to treatment.

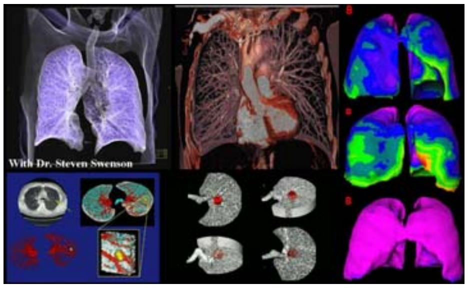

Figure 21. 3D and 4D volume imaging in assessment of pulmonary disease. Lung volumes, tumor locations and sizes, blood and air flow distributions and biophysical properties can be computed and mapped on lung surface, such as normal (top right), focal asthma (center right) and emphysema (bottom right).

One of the most successful and important clinical applications of 3D medical imaging and volume rendering is virtual endoscopy. Virtual endoscopy has the advantage of noninvasive exploration of body cavities, which may be useful in screening procedures. Figure 22 shows an example of virtual colonoscopy – endoscopic views within the colon computed from a fast spiral CT scan of the abdomen of a patient with colonic polyps. The precise location, geometry and composition of the polyp can be measured from the correlated raw CT data to help determine metastatic potential of the polyp and help guide therapeutic decisions.

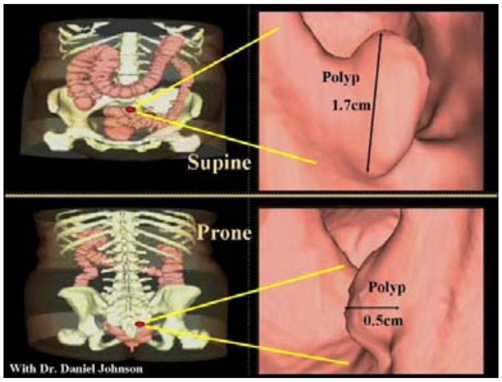

Figure 22. Virtual colonoscopy reveals polyps, their location, size, and composition from high resolution 3D CT scans.

Prostate brachytherapy is being used more often to treat prostate cancer in deference to the morbidity and risk associated with radical prostatectomies. In prostate brachytherapy, radioactive seeds are implanted throughout the prostate in a pattern designed to provide maximal kill to the cancer while sparing critical normal structures, such as the urethra and urinary sphincter. We have developed online real-time transurethral ultrasound (TUUS) imaging to monitor the seed deposition process. The 3D ultrasound images are registered with fluoroscopy to localize the seeds, reconstruct them in three dimensions, account for seed aggregates, and from these compute online the volume dose distribution. Any cold spots can be filled immediately if necessary. The on-line dosimetry can be compared with the pre-treatment dose plan to help improve planning for optimal distributions. Figure 23 is an illustration of this image-guided prostate brachytherapy procedure.

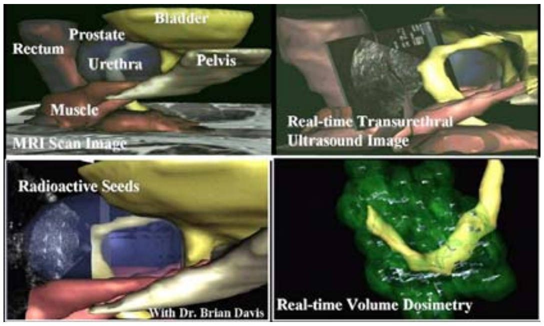

Figure 23. 3D anatomical model of prostate and adjacent tissues computed from MRI scans to visualize tumors, guide optimal deposition of radiation seeds and facilitate on-line dosimetry.

4. THE FANTASTIC FUTURE – PREDICTIONS

There are significant forces for change facing medicine in the 21st Century and beyond. We have moved into an era where the individual is empowered as never before in making choices regarding his or her lifestyle, including health care. This consumer empowerment combines with current significant advances in information capture and communication, accelerated scientific discovery and developments, and rapid deployment of technology, to present both the best of times and the worst of times in anticipating the future.

Without doubt, one of the most promising recent developments, which is going to expand into the future, is molecular imaging. Molecular imaging is biomedical imaging combined with genomics, and perhaps proteomics and physiomics. Molecular imaging involves imaging the alterations in molecular confirmations that are the basis of disease, rather than merely observations of pathological effects, as generally done in current medical imaging. Molecular imaging is going to provide the capability for imaging selective gene expressions and finding new markers for early disease detection, and this will lead to very specific markers for administering therapy and for assessing the effectiveness of therapy.

There will be some barriers to progress. Foremost among them are communication and education, development of acceptable wide spread standards and databases, natural and robust and effective graphics interfaces tailored to specific users, validation and adoption of ever-improving and refined technology, and perhaps most importantly, the successful transfer of technology into the marketplace. I will briefly address each one of these challenges.

Regarding communication, we have to overcome some legacy constraints, that is overcoming the dogma of 3D mental reconstruction as acceptable, opposed to actual computed reconstruction; overcoming the misperception that three- and four-dimensional images cannot provide more information than available from projection or serial 2D images alone, and overcoming cross-disciplinary culture clashes. The disciplines of biological sciences and engineering must meld with clinical science and clinical practice in effective and synergistic ways. Biomedical Engineering may be the force to glue together these disciplines. Researchers in the field who make great scientific discoveries and advances need to be open and willing to share these discoveries and to encourage and educate other workers and students in the same field of scientific research.

The problem with standards is that we have so many of them! DICOM has evolved to become a useful standard in medicine, but it is not perfect. There are not similar standards in computer programming and sharing of code and internet communications. These need to be developed, and this will in turn empower and facilitate more rapid advances in the scientific and medical communities.

There is a need for normative image databases and pathology databases and digital image collections of a wide variety that must be organized and preserved and made freely available. The ability to reproduce published results from archived data, and effective tools to do this, need to be developed. There needs to be ready transparency and ease of use and quality of service and robustness in reproducibility of the information in these databases. The information infrastructure that includes images and integrates them with all associated meta data needs to be developed.

The user interface is often the most neglected, least optimal component of an imaging system. Open standards for developing interfaces and modifying them and tailoring them to specific applications need to be established, and much more time needs to be spent on optimal interface design. User interfaces need to be carefully organized and managed with frequent reviews. The standard steps are to 1) do a thorough application analysis, 2) complete a dialogue design, 3) complete a graphic design, 4) do iterative prototyping, 5) conduct a robust evaluation of usability, and 6) feed back information into all the other steps to evolve, through as many iterations as necessary, an optimal user interface that facilitates efficient and effective use of the technology that underlies the system.

With regard to validation, both scientific and clinical evaluation methods need to be used to move technology from the laboratory and the research bench to the hospital and the patient bedside. Table 2 is a list of both objective and subjective validation factors that should be considered in getting useful technology into the hands of medical practitioners. These factors have been evaluated over and over again, and provide a canonical set of axioms to use in evaluating new advances to render them available and acceptable in the practice arena. The last of these, exclusivity, means that if the new method is unique and highly meritorious in one or more applications, then academia and industry and government and insurance providers must work expediently together to rapidly make it available to treat the suffering patient.

Table 2: Validation Axioms

1. Objective Factors to Measure
   - Sensitivity and specificity
   - Reproducibility
   - False positives and negatives
   - Conformance with standards
   - Time and cost
   - Outcome (survival/morbidity)

2. Subjective Factors to Characterize
   - Physician acceptance
   - Patient acceptance
   - Government acceptance
   - Insurance company acceptance
   - Exclusivity (unique merits)

Technology transfer to the marketplace needs to be based on several important considerations as well. Some of these are listed in Table 3.

Table 3: Technology Transfer Requirements

- Based on relevant needs and expectations
- Improves outcomes and/or reduces risk
- Computationally and procedurally safe
- Accurate, reliable, easy to use
- Modular, extensible, portable
- Maintainable and supportable
- Scientifically and clinically validated
- Cost benefit analysis favorable

The clinical forecast regarding value of truly useful nanotechnology is clear. To quote one Mayo Clinic surgeon: *"Advanced imaging and visualization technology and minimally invasive interventions will significantly impact the practice of surgery by providing improved validation and interpretation of diagnostic images, reduced time in the operating room, greater surgical precision, all improving outcomes, minimizing morbidity, and reducing costs."*

The elements for progress into the future are the same now as they have been in the past. We move from the past to the future with a combination of ideas and tools. Ideas without tools are not enough. Tools not based on good relevant ideas will not endure. More and more, the work needs to be accomplished by multidisciplinary teams. No individual has sufficient expertise and access to the requisite knowledge and information and processes to accomplish alone the advances in technology required.

The future is indeed bright, and perhaps beyond our full ability to accurately comprehend and fully appreciate. Table 4 is a brief summary of some of the developments we may anticipate over the next several decades in medical imaging and medical technology.

Table 4: Predicted Advances in Biomedical Imaging

- Real-time, on-line, minimally invasive technology
  – Synchronous diagnosis and treatment
- Several new imaging modalities
  – Molecular and biochemical imaging
- Vastly intelligent instruments and robots
  – In-vivo seek, treat and monitor "nanobots"
- Smarter clothes and rooms
  – Full body sensing and tool tracking
- Hand-held supercomputers
  – Voice recognition, natural control, real-time models
- Scale space fusion
  – Real-time integration – macro to micro, structure to function

New imaging devices we have not yet thought of will be developed. These will completely and quantitatively reveal all biological, molecular and chemical actions, interactions and reactions. Multidimensional dynamic displays, image gloves for hands-free navigation in virtual space and voice control will epitomize the next generation of enhanced reality medical procedures. Intelligent rooms and clothing that perform real-time tracking and monitoring will provide comprehensive and instantaneous input for informed, even automated, decision making. Special high precision robots, remotely controllable, will establish routine practical use of telemedicine and teletherapy. Real-time model generation and programming computers in natural language will be possible, and super computers will, in fact, be small or even nano-sized, and used both outside and inside the body. Intelligent diagnostic and/or therapeutic probes will be introduced into the body in either pre-programmed or externally controlled modes to direct navigation to the anatomic site of interest for focused diagnosis, treatment and/or monitoring. Eventually we will have the kind of totally non-invasive real-time technology that presently resides in the realm of science fiction, but the future indeed holds great promise for development of devices and procedures that simultaneously perform diagnosis and treatment – sort of one stop shopping. The proposed door to the future may be such a device, but this author believes it will be much smaller than a door, more like powerful flashlights and flood lamps.

A major goal will be to integrate and synthesize ("scale space fusion") for visualization and quantitative analysis both structure and function of living objects from image datasets that span a wide range of scale – from molecules and cells to tissues and organs to complete physiological systems. One endpoint of this effort will be to realize what one might call "full synthetic reality". This means visualization of all objects of interest, regardless of dimensional size and/or separation, that is sufficiently accurate and faithful so as to render the virtual representations indistinguishable from the real objects. Traversing the distances between these virtual objects and appropriately scaling their local environment to relevant dimensions will be automatic and instantaneous. Then simulations which teach, train, rehearse, augment or help carry out medical diagnostic and therapeutic procedures will become truly useful and ubiquitous. With the expected advances and miniaturization of powerful computing and electronic sensing elements, imaging devices will continue to improve in resolution, speed and affordability and will be deployed harmlessly within the body as well as outside of it.

5. CONCLUSION

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The history of biomedical imaging has been rich in technological advances. The present capabilities are outstanding and foretell a fantastic future we can barely imagine. But we must keep one foot on the firm ground of practicality as we look to the uncertain horizon of the future. Important ongoing needs in biomedical imaging include: 1) increased multidimensional resolution through space and time of images, procedures and devices, 2) automatic accurate anatomic and functional segmentation from image data produced by medical volume scanners of the human body, 3) fast and robust multidimensional image registration and fusion, 4) faithful tissue feature and property classification, and 5) realistic real-time volume rendering and visualization. Progress in these areas will have an ever-increasing positive impact on medicine and healthcare.

There are some cautions to be raised. One of the major pitfalls that any technology age suffers is that there are more false prophets than true pioneers (the author asserts to be neither). We have to more expediently discern those that are *"full of sound and fury, signifying nothing"* (Shakespeare's MacBeth) vs. those that are truly innovative scientists and engineers. At any given moment in history it may be challenging to identify the false prophet from the true pioneer. John Lawton said *"The irony of the information age is that it has given new responsibility to uninformed opinion"*. I agree with this. We are indeed in the age of information, for better and for worse. It is, in fact, the age of information glut, so enormous is its magnitude and ready availability. We are not well poised to take maximum advantage of the ever-growing repository of available information. To compensate, some shortcuts are taken by the false prophets, resulting in deductions that are not substantiated by good hard facts and experimentation. Again, we need validation, validation, validation.

The cost of new technology should not be the driving nor limiting factor to future progress. It is important, but if the cost of developing and proving a new technology can be demonstrated with high probability to improve and impact positively healthcare and eventually reduce costs, then fortitude and foresight must prevail to make the required capital investment. There is ample room in the field for true pioneers and visionaries. Indeed, they are always needed. But there is also need for rationale practitioners who exercise common sense and are committed to reduction to practice. As Carl Popper said *"I hold it to be morally wrong not to believe in reality."* The degree to which virtual reality (including biomedical imaging and modeling) will ultimately be successful in improving healthcare and advancing the state-of-the-art in medicine will surely be commensurate with the degree to which we understand reality and are sensitive to it. The reason for this is simple. The object of medicine is the patient, and the patient is real. But we move forward toward the stars. Star Trek, here we come.

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7. REFERENCES

[1] R.A. Robb, J.F. Greenleaf, E.L. Ritman, S.A. Johnson, J.D. Sjostrand, G.T. Herman, and E.H. Wood, "Three-dimensional visualization of the intact thorax and contents: A technique for cross-sectional reconstruction from multiplanar x-ray views", *Computers and Biomedical Research,* 7:395-419, 1974.

[2] R.A. Robb, and E.L. Ritman, "High-speed synchronous volume computed tomography of the heart**",** *Radiology,* 133:655-661 (December) 1979.

[3] R.A Robb, "X-ray computed tomography: From basic principles to applications**",** *Annual Reviews in Biophysics and Bioengineering*, 11:177-201, 1982.

[4] R.A. Robb, *Three-Dimensional Biomedical Imaging***, C**RC Press, Inc., Boca Raton, FL, Vols. I & II, 1985.

[5] R.A. Robb, and C. Barillot, "Interactive display and analysis of 3-D medical images**",** *IEEE Transactions on Medical Imaging*, 8(3):217-226, 1989.

[6] R.A. Robb, *Three-Dimensional Biomedical Imaging - Principles and Practice,* VCH Publishers, New York, NY 1995.

[7] R.A. Robb, *Biomedical Imaging, Visualization and Analysis*, John Wiley and Sons, Inc., New York, NY, 1999.

[8] R.A. Robb, "Virtual endoscopy: Development and evaluation using the Visible Human Datasets", *Computerized Medical Imaging and Graphics*, 24:133-151, 2000.

[9] R.A. Robb, "The Biomedical Imaging Resource at Mayo Clinic", Special Editorial in *IEEE Transactions on Medical Imaging*, 20(9):854-867, 2001.

[10] R.A. Robb, "Virtual Reality in Medicine: A Personal Perspective", *Japan Journal of Visualization*, 5(4):317-326, 2002.