MEDICAL COMPUTING

A computer in one form or another is present in almost every instrument used for making measurements or delivering

therapeutic or experimental interventions in clinical practice, clinical research, or in any of the fields of the biomedical sciences. In some cases, the computer is a chip that is embedded somewhere in the instrument, and the user has little indication that he or she is actually interacting with a central processing unit (CPU). In other cases, the form of the computer is an engineering workstation or a personal computer with keyboard, mouse, and the other accoutrements that are normally associated with the act of "computing." In either case, the computer allows the accomplishment of tasks that were impossible or overwhelmingly difficult without the use of this ubiquitous technology.

Many of the concepts that were implemented in early computers are still routinely used in modern devices, but with vastly different technological bases. Most digital computers have traditional architectures, with separate memories, central processing units, and input/output and storage devices. A major difference is the miniaturization and increased efficiency of electronics devices, including computers, which have allowed the development of sophisticated medical therapeutic options that can be totally implanted in the body. The increased sophistication of computers has also led to vastly improved user interfaces and quality control in all kinds of medical instruments.

This article reviews some of the historical and contemporary computer applications in medicine and biomedical research, from real-time applications to medical informatics to virtual reality. These applications are as diverse as the physical form of the computer on which they are implemented. They include: real-time signal acquisition and subsequent processing; efficient storage and manipulation of enormous databases for large-scale clinical trials and other clinical and basic research; assistance in clinical decision-making; acquisition, processing, and transmission of diagnostic images from a wide range of technologies; simulation and display of two- and three- dimensional structures and function; animated displays of physiological processes; and access to educational and promotional medical information. Of course, any discussion of the use of computers in biomedicine would be incomplete without reference to the explosion in the use of the Internet for electronic mail, news, and World Wide Web access. Many of these topics will be briefly mentioned; specific applications will be more completely described as examples of how computers can be used to improve medical practice through broadening the scientific underpinnings and making new techniques available to practitioners. Many applications that are implemented on computers will be more fully developed in other articles of this encyclopedia.

MEDICAL INFORMATICS

The study of the use of computers in medicine is often called "medical informatics." Medical informatics has been termed "an emerging discipline that has been defined as the study, invention, and implementation of structures and algorithms to improve communication, understanding, and management of medical information (1)." (Further information can be found on the newsgroup *sci.med.informatics*). This broad area comprises many of the subjects included in medical computing, and there is a vast literature on ways in which computers improve health care delivery through aids in organizing, accessing, and presenting knowledge. Medical informatics is concerned with the flow of medical information, and how data that can be used in the effective diagnosis and treatment of disease can be made available in a timely fashion and in a format that will provide the most usefulness (2). The integration of medical information systems into routine clinical activities has not been fully achieved (3).

Efficient organization and delivery of biological and medical information have assumed new importance with the explosion in knowledge about the genetic and molecular bases of disease. One of the grand challenges of computing is the deciphering of the human genome, and sophisticated computer algorithms have been developed for identifying genes embedded in long DNA sequences (4). A recent issue of the journal *Science* described some of the opportunities for the application of computers in several areas of medical and biological research. Articles in the aforementioned issue described new approaches to searching the World Wide Web as a digital medical library (5), the application of computing to mathematical ecological studies (6), and the use of a massive database for investigating the relationship between pharmacological agents and cancer (7). In general, the Internet, including news groups and World Wide Web sites, has been a rich resource for all kinds of medical information (8,9); indeed, the challenge is to develop methods for accessing the data in ways that are intuitive and accurate. For example, a system has been written to exploit effectively the digital images of human anatomy that are stored on the Web (10). Figure 1 is an example of a workstation screen from this system which allows flexible interrogation of three-dimensional anatomical databases, providing access to this wealth of information for users without detailed knowledge of computer and database architectures.

The study of artificial intelligence and expert systems is also typically considered a central theme of medical informatics. These systems use learning and advisory strategies to assist in decisions related to diagnosis and therapy of human disease. One of the earliest results in expert systems was the computer program named *MYCIN,* which was designed to assist physicians in the selection of antimicrobial agents for hospital patients with bacterial infections (11). Artificial neural networks have been used to assist in the detection of patterns in clinical data and associate them with clinical conditions and outcomes (12,13). Human beings are quite adept at incorporating uncertainties in their reasoning, but computers have been viewed as unforgiving in the face of ambiguities. The theories of fuzzy sets and fuzzy logic (14) have been developed to address this discrepancy, and they have attracted attention for their wide applicability (15). They have been used in classification of biomedical signals (16) and analysis of biomedical images (17). The study of expert systems is an active area of investigation in the application of computers to medicine.

SIGNAL ACQUISITION AND ANALYSIS

One of the earliest applications of computers in medicine and medical science was their use for acquiring, analyzing, and displaying waveforms that reflect physiological and pathological processes. Prominent examples include the electrocardiogram (ECG) and electroencephalogram (EEG), which record the manifestations at the body surface of the electrical gener-

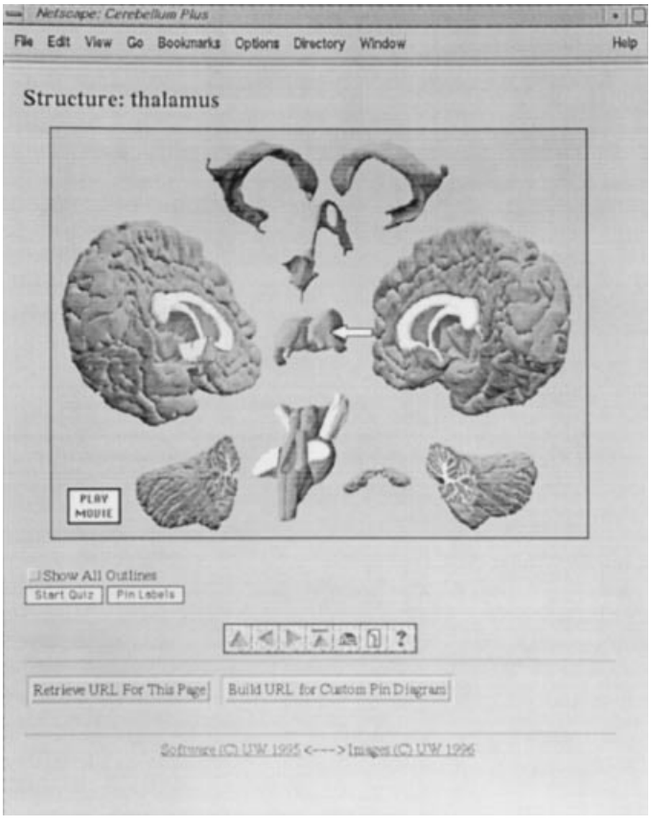

Figure 1. Computer screen from the "Digital Anatomist Information System (10)," an interactive query system for access to three-dimensional anatomic databases using Internet browser principles. This display allows the user to identify particular structures of the brain, in this case the thalamus, by selecting the region of interest with the computer input device. Reprinted from Ref. 10, with permission.

ators in the heart and brain, respectively. For computer analysis, it is necessary to sample the waveform and convert it from analog to digital format (18). In electrocardiology, computers have been used for the analysis of clinical ECGs to identify patterns in the waveform that reflected underlying disorders of electrical activation or structural heart disease (19,20). Similarly, patterns in EEGs have been correlated with normal neurophysiology and with pathologies such as epilepsy (21). Commercial systems are based on similar analyses and are widely used in hospitals and clinics for diagnosing cardiac and neurological abnormalities.

At the same time, the use of computers has expanded the level of investigations that are possible in attempting to understand the scientific basis of normal and abnormal physiological function. Even though much was learned about cardiac electrophysiology by using instruments like string galvanometers (22), improved technology and the application of digital computers have allowed measurements to be made in situations that were not accessible to earlier investigators. For example, it is now possible to record from hundreds of sites on the surface of the heart and within the cardiac tissue to assemble a high-resolution reconstruction of the intrinsic or externally generated bioelectric events in the myocardium (23). Cardiac mapping studies that acquire data from many sites simultaneously have shown that there is considerable order in heart rhythms formerly thought to be completely disorganized (24,25). Figure 2 is an example of a signal processing result that demonstrates that electrograms recorded from a rectangular array during ventricular fibrillation have a great deal of organization even when they are recorded from sites separated by as much as 5 mm to 11 mm. Thus, computer-based multichannel acquisition and analysis of cardiac arrhythmias have revealed phenomena that might be crucial in the improved prevention and treatment of these often fatal derangements of rhythm.

Multichannel recording from the brain using computer-based systems has resulted in new insights into the way in which the brain's electrophysiological and psychological functions are organized (26). Similar systems have been developed to study the electrical activity associated with the gastrointestinal (27), genitourinary (28), and reproductive (29) systems.

The development and implementation on computers of the fast Fourier transform has allowed the examination of biosignals in the frequency domain, opening the doors for new insight into mechanisms of important clinical entities (30). Spectral methods allow the elucidation of relationships between different physiological systems (31). Wavelet theory has further extended the application of frequency domain techniques by avoiding the limitations imposed by discrete Fourier analysis (32). Wavelets have been applied to electrocardiography, to detect irregularities in heart rhythm; to pho-

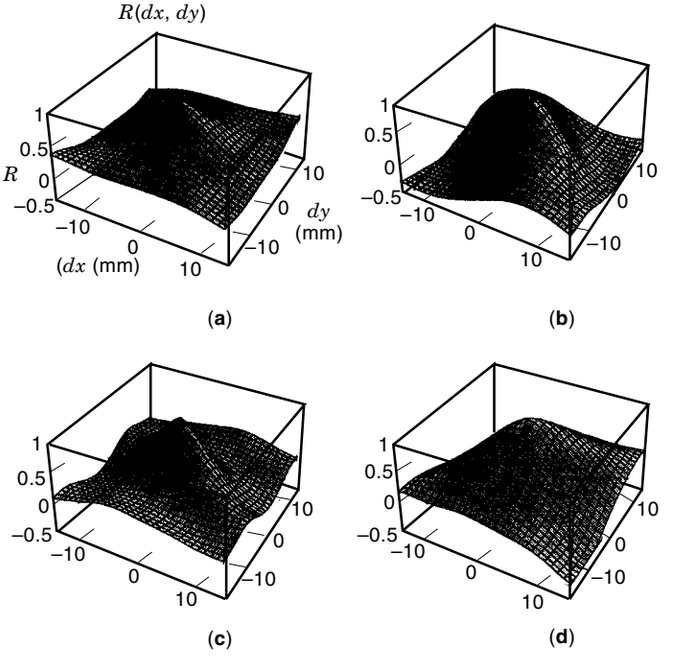

Figure 2. Plots of correlation coefficient between two electrograms recorded from a rectangular plaque array on the ventricular epicardium of a pig during ventricular fibrillation. Panels a to d are data from 1 s to 2 s; 2 s to 3 s; 3 s to 4 s; and 60 s to 61 s after the induction of ventricular fibrillation. The electrical activity in two electrodes appears to be well correlated, out to a distance between recording sites of about 5 mm to 7 mm, but this distance changes as fibrillation continues. Whereas fibrillation has traditionally been considered to be a completely disorganized rhythm, computer-based signal processing techniques have revealed substantial levels of order. Reprinted from Ref. 24, with permission.

nocardiology, to analyze heart sounds in search of turbulence associated with obstructions in coronary vessels; to examine the EEG for evidence of fetal respiratory abnormalities; and in image analysis and compression (32).

COMPUTER-BASED DEVICES

Many medical devices require the acquisition and analysis of analog signals or variables that reflect underlying physiological processes. Typically, a method is developed to transduce the variable of interest to a voltage which can then be converted to digital form and analyzed. The implementation of these systems ranges from integrated chips with analog electronics, analog-to-digital converters, and some signal processing capabilities included to general-purpose computers with specialized or general-purpose electronics designed to carry out these functions. The devices are used in physiological and biomedical research and in instruments used for making clinical decisions. The computers are often used as control systems as well as data acquisition devices, with or without closed-loop feedback.

Embedded Computers

Figure 3 is an example of a highly specialized medical device, the implantable cardioverter-defibrillator, with a fully functional computer embedded in it. The function of this device is to monitor continuously the electrical signal derived from electrodes in contact with the heart, detect the onset of abnormalities in cardiac rhythm that are candidates for treatment, and deliver appropriate therapy. To carry out this role effectively, it is necessary for the instrument to sample and digitize the cardiac electrograms with sufficient accuracy to allow morphological analysis; identify the time at which the electrical wave passes the electrode in order to compute R–R intervals and, thus, heart rate, often with analog processing (33); distinguish between normal rhythms and categories of arrhythmias that require different levels of therapy (34); and control delivery of antitachycardia pacing or a defibrillation shock.

Figure 3(a) is a photograph of such a device. It is intended for implantation beneath the clavicle in patients who are at high risk for sudden cardiac death. In use, leads are directed from the header through the venous system into the right ventricle of the heart. There are electrodes on the catheters for sensing the cardiac activity and delivering energy. Figure 3(b) is a photograph of the die of the microprocessor that is in the defibrillator. The demands on this circuit are extraordinarily stringent, since a malfunction in either software or hardware is likely to be fatal to the patient wearing it. The validation of the operation of the computer is obviously of utmost concern to the manufacturer, the implanting physician, regulatory agencies, and, especially, the patient.

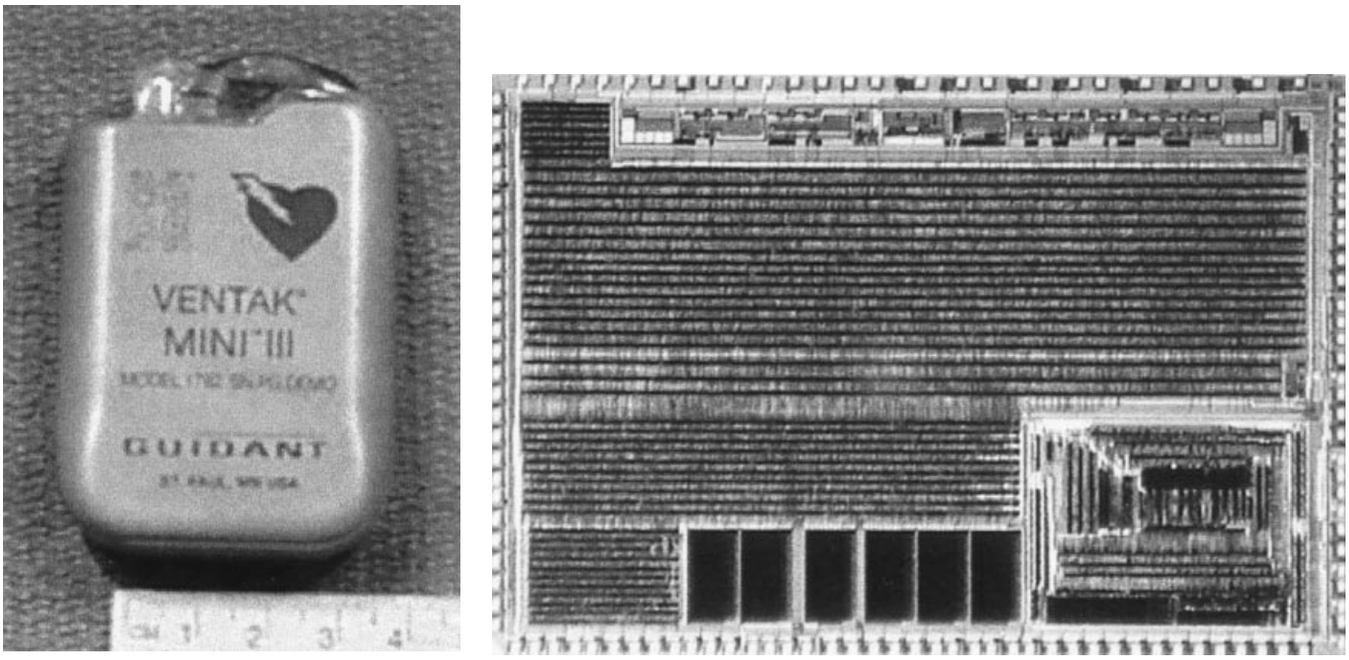

Figure 3. (a) Photograph of a mockup of an implantable cardioverter-defibrillator. The device is implanted under the clavicular region of a patient who is at high risk of sudden cardiac death. The overall dimensions of the device are $4.5 \times 7 \times 1.25$ cm. (b) A photograph of a die of a digital computer system that is contained in the device shown in panel a. The dimension of the chip that is fabricated from this die is 12.8 by 7.7 mm. The chip, with 2 μ interconnecting lines, contains about 150,000 transistors. In addition to a typical microprocessor, the system contains sense amplifiers, a digital control section for analyzing cardiac electrical activity and initiating therapy when necessary, five banks of 1 Kb read-only memory, and circuits for telemetering data to and from the external world. Photograph courtesy of CPI/Guidant Corporation.

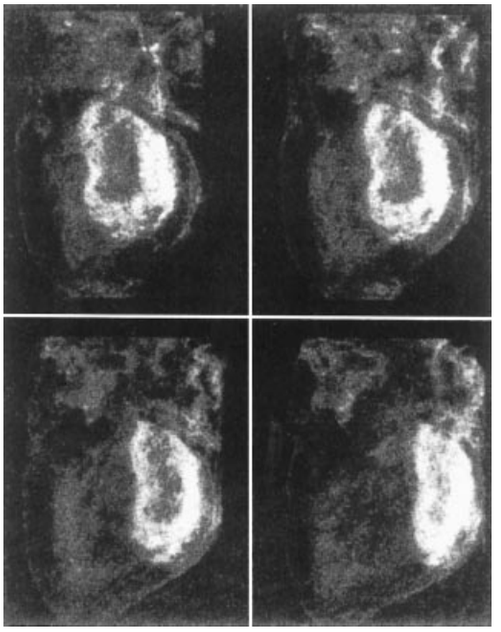

Figure 4. A ray-traced, volume-rendered magnetic resonance image of a canine heart with a myocardial infarction. The image was acquired from a postmortem, formalin-fixed heart after a study to determine whether necrotic tissue could be reliably detected by MRI. Computer-based magnetic resonance microscopy can be used for diagnosis and evaluation of pathology, as well as for investigations into the interplay of structure and function in clinical and experimental studies. Reprinted from Ref. 35, with permission.

Computers are often embedded in other medical instruments that do not play as acutely critical a role as do implanted devices, but are very important in assessing health and disease. For example, a blood gas or electrolyte analyzer might have a microprocessor that controls the user interface, calibration procedures, and data acquisition, analysis, and display. The widespread use of microcomputers in these analyzers provides convenient access to functions such as calibration and standardization that previously were time-consuming and labor-intensive.

Stand-Alone Computers

Other medical instruments are based on general-purpose computers, typically engineering workstations. Examples of these are large imaging systems, such as magnetic resonance imaging (MRI) or computed tomography (CT) systems. In these cases, the computer fulfills a variety of roles. In MRI systems, the computer can provide the user interface to the highly specialized and complex hardware associated with the magnet. The echo sequences that determine the imaging parameters and quality can be controlled through the computer as a front end. These workstations often contain high-performance image processing and graphics hardware that can be used for manipulation of the acquired images and display of the results to the clinician in intuitive, usable formats. Figure 4 is a volume-rendered, ray-traced magnetic resonance image of a canine heart with an experimentally induced myocardial infarction (35). This image was generated on a high-performance workstation, and it demonstrates the kinds of displays that provide users with scientifically and clinically useful information. Furthermore, the workstation and associated peripheral devices can be used as archival storage systems for managing the overwhelming amounts of data that are generated by modern imaging modalities.

The computers associated with these clinical systems can be networked using industry standard hardware and software to provide convenient access to remote sites, either within a hospital or medical center or outside the center to a referring physician or a specialist who might have more experience in interpreting certain imaging results. This is an example of the interaction between medical imaging and telemedicine (36), often thought of as one of the subdisciplines of medical informatics.

COMPUTER GRAPHICS AND MEDICINE

Another early use of computers in medicine was the application of graphics systems for the acquisition and realistic display of anatomic structures in research and clinical situations. Much of the emphasis has been on two- and three-dimensional reconstructions of data from medical imaging modalities. Early work focused on the use of computers to estimate cardiac function from single- and dual-plane cineangiography (37), as well as estimate the reconstruction of coronary artery anatomy from coronary arteriograms (38,39). As medical imaging technologies have advanced, the computational demands for extracting new information from image analysis and displaying the data in realistic ways have increased. Substantial portions of the techniques developed for nonmedical applications are not immediately applicable to biological and physiological systems because of the inherent variability and irregularity that are not present in, for example, computer-aided design/computer-aided manufacturing (CAD/CAM) structures (40). Another problem that is unique to medical applications is the recent emphasis on reducing health care costs, limiting the unfettered introduction of new technologies (40). At times, there is a problem with the integration of creative, novel algorithms to a community that is sometimes reluctant to modify procedures that have been established as effective, comfortable, and productive (3).

Image Processing

Most of the images from modern techniques, including digital radiography, magnetic resonance imaging, computed axial tomography, and ultrasound imaging, require similar procedures for the production of usable graphics displays. Often, the first step is the segmentation of the images, or the identification of different structures. Much work has been done on computer-based segmentation, and currently most approaches use basically automatic systems with varying amounts of manual editing of the results. There is a wide variety of segmentation algorithms, and many of them have been implemented in readily available software packages. In general, the imaging devices yield two-dimensional images, with $M \times N$ picture elements, or pixels, where M and N are the number of pixels in the horizontal and vertical dimensions, respectively. Typical image sizes are around 256×256. Image resolution, the number of pixels per length, is then determined by the size of the field of view of the device. The computational demands of image processing algorithms in-

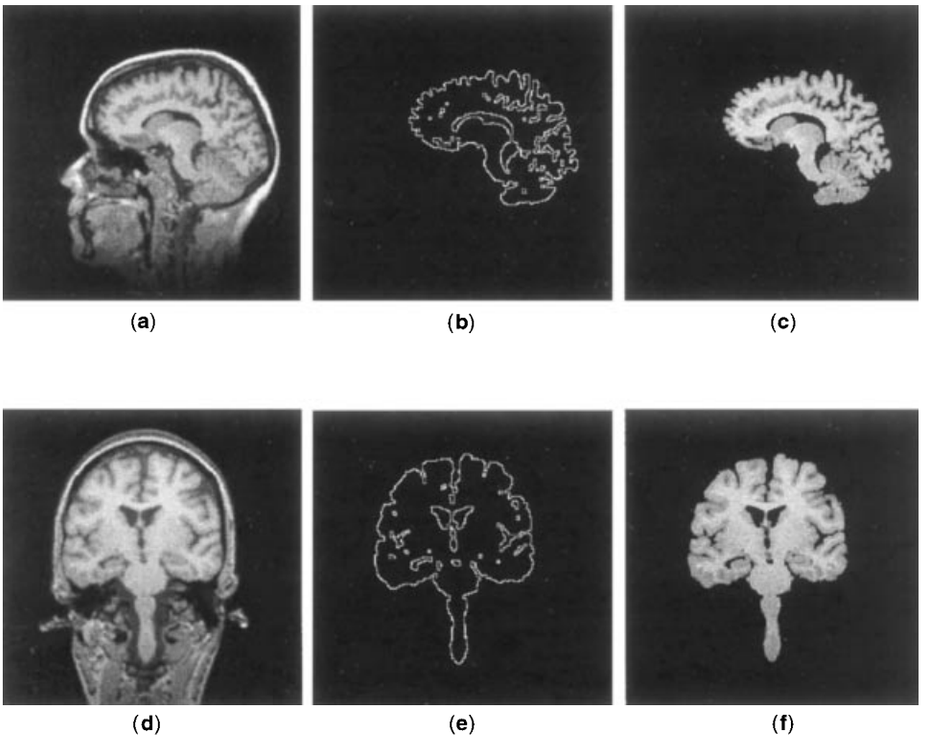

Figure 5. Sagittal (a) and coronal (b) magnetic resonance images of the head. The left two panels are the original images. The middle panels show the outline of the brain as detected by an automatic three dimensional segmentation algorithm. The right panels are the portions of the images that are within the detected brain outline. Reprinted from Ref. 42, with permission.

crease drastically with increasing resolution, since processing generally increases with the square of the resolution for two-dimensional images or as the cube of the resolution for volume analyses.

Each pixel is usually comprised of eight or more bits, each combination of which represents a gray level. The value of the gray level is determined by the method by which the image is formed. For example, in CT scans and radiographs, the intensity of the pixels reflect whether the photons have passed through bone or soft tissue. Magnetic resonance images detect differences in water content in organs and can provide different kinds of information from CT scans. In any case, segmentation algorithms must manually, automatically, or semiautomatically detect the transition from one level of intensity to another (41). Some are based on region growing methods, in which a seed is provided and a region of similar intensities is expanded until the level of the pixel intensities changes beyond a preset limit. Others are based on discontinuities in the pixel intensities, often computing the gradients of the intensities and changing tissue classifications based on the magnitude of the gradient. Figure 5 is a two-dimensional projection of a three-dimensional magnetic resonance image of a head. The brain tissue has been separated from non- brain using a three-dimensional seed growing algorithm (42). The automatic segmentation of images from the various medical imaging technologies remains an active area of research (41).

Modern imaging technologies routinely provide three-dimensional anatomic information (35), and the demands on image processing programs have increased correspondingly. The underlying principles are similar, but the computational constraints become more severe. In addition, even though storage and networking technologies are progressing quite rapidly, image processing software must often incorporate data compression and decompression capabilities to accommodate extension of images from two to three dimensions, the increased image resolutions achievable with modern devices, and the need to transmit large datasets over networks.

Computer Graphics

Intimately related to the issues of image processing are the techniques by which medical and biological images are displayed with enough realism to achieve the intended results but with enough efficiency to be used in actual clinical situations. Algorithms and programs for accurately portraying anatomy and, to some extent, function have improved steadily, sometimes exceeding the ability of the hardware to meet the demands. Fortunately, the well-known advances in performance and cost of advanced graphics hardware, including general-purpose computers as well as special-purpose graphics processors, have provided the platforms necessary for implementation of state-of-the-art graphics techniques.

The display of two-dimensional images is, in principle, straightforward on a computer output screen with multiple colors or gray levels per pixel. The display programs provide an interface between the user, the image, and the graphics hardware and software of the computer so that one pixel of the image is translated to one pixel of the video screen. Complications arise when there is a mismatch between the image and the screen, so that image pixels must be removed or display pixels must be interpolated. A further complication for the developer of either two- or three-dimensional graphics software is the plethora of data file formats that exist (43). Fortunately, many public domain or proprietary software packages provide excellent format conversion tools, but some experimentation is frequently required to use them properly.

The development of methods for efficient and realistic rendering of three-dimensional images continues to be an area of ongoing research. Early work reduced anatomic structures to wire frame models (44), and that technique is still sometimes used for previewing and rapid manipulation on hardware that is not sufficiently powerful for handling full images in real time or near real time. Several methods require the identification of surfaces through image segmentation, as described above. The surfaces can be triangulated and displayed as essentially two-dimensional structures in three dimensions (45). After initial processing, this is a rather efficient display method, but much of the three-dimensional information is lost. Alternately, the image can be reduced to a series of volumetric structures that can be rendered by hardware specialized for their reproduction (46). One of the most realistic, but computationally expensive, three-dimensional rendering methods is ray tracing, in which an imaginary ray of light is sent through the structures and is attenuated by the opacity of the anatomic structures that it encounters along the way (47). Different effects can be emphasized by modifying the dynamic range of the pixels in the image—that is, by changing the relationship between the opacity of the image and the pixel value to be displayed on the screen.

Medical computer graphics are at their most useful when it is possible to superimpose images from more than one modality into a single display or to superimpose functional information acquired from biochemical, electrical, thermal, or other devices onto anatomical renderings. As an example of the former, images from positron emission tomography (PET) scans, which reflect metabolic activity, can be displayed on anatomy acquired by magnetic resonance imaging. The combination provides a powerful correlation between structure and function, but the technical challenges of registering images from two different devices or taken at different times are significant (48). An example of the combination of functional and anatomic data is the superposition of electrical activity, either intrinsic or externally applied, of the heart onto realistic cardiac anatomy. This kind of technique can provide new insights into the mechanisms and therapy of cardiac arrhythmias (49). Figure 6 is a sequence of still frames from a video showing the progression of a wavefront of electrical activation across a three-dimensional cardiac left ventricle after an unsuccessful defibrillation shock.

Computer graphics and image processing, along with advanced imaging technologies, are making a significant impact in medical knowledge and practice and have the potential for many more applications. A combination of traditional CAD/CAM visualization and advanced imaging can be used for effective assessment of quality of fit of orthopedic prostheses (50). Capabilities and functionality have increased dramatically with the advent of advanced graphics hardware and commercial software packages aimed at scientists and clinicians who are not graphics experts. Full realization of the benefits of these systems will require further advances in these areas, along with adaptation to the needs of clinicians and the constraints of the changing health care climate (51).

COMPUTER SIMULATIONS

Numerical and analytical simulations of physiological processes have intrigued investigators for many decades. The solution of inverse and forward problems in neurophysiology and electrocardiology was considered to be an important exer-

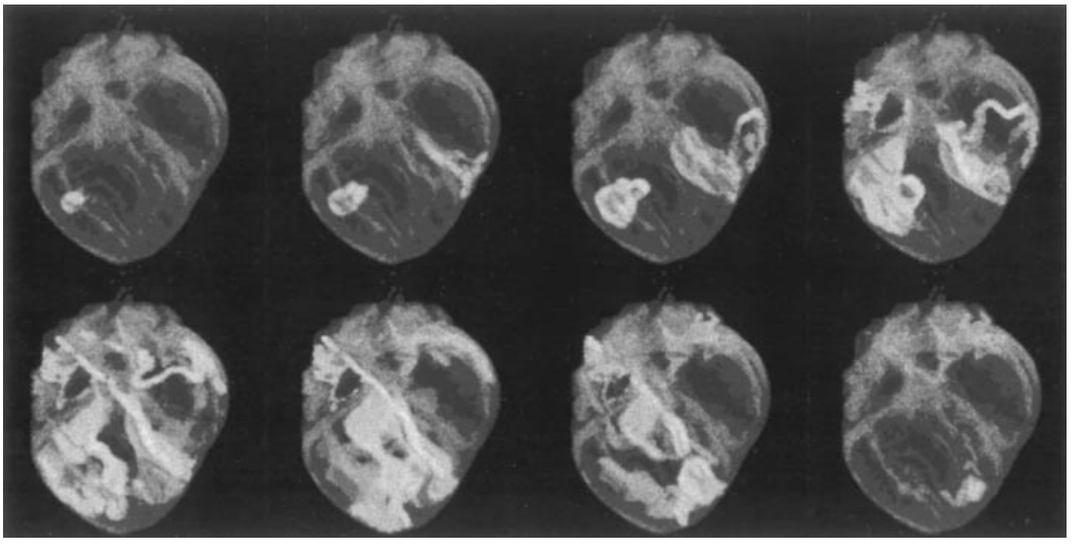

Figure 6. A composite of eight magnetic resonance and isochronal surface images from the second activation wavefront after an unsuccessful defibrillation shock. The electrical data were acquired from about 60 plunge needles with endocardial and epicardial electrodes inserted through the left and right ventricles of the heart of an experimental animal. Successive isochrones (left to right, top to bottom) are shown at 6 ms intervals. Visualization techniques that allow the superposition of function and anatomy are very helpful in understanding the relationships between variables and how they affect physiological mechanisms, and they can potentially lead to improved diagnosis and therapy. Reprinted from Ref. 49, with permission. Copyright CRC Press, Boca Raton, FL.

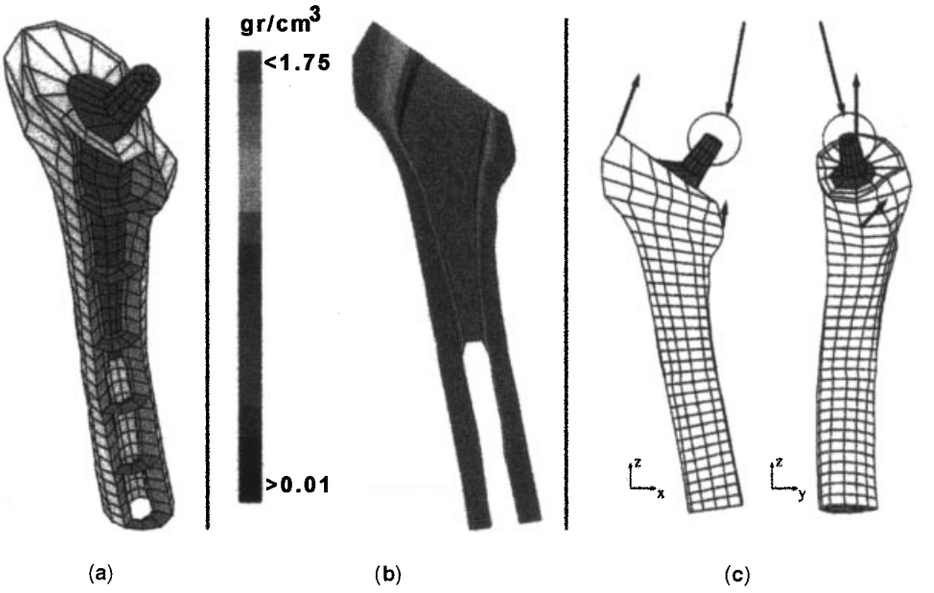

Figure 7. Display of a model of a femur used to study adaptation of bone in response to a stimulus. (a) A finite element mesh of proximal femur with stem of prosthesis numerically implemented for optimal fit. (b) Bone density distribution in the femur at initial implant. (c) Applied and muscle forces in the femoral head with prosthesis in place. Reprinted from Ref. 67, with permission. Copyright Gordon and Breach Publishers, Lausanne, Switzerland.

cise for basic scientific reasons as well as for possible clinical applications. The interpretation of the surface signals recorded in the context of approximate generators in the tissue provided a basis for relating physiology to pathologic and clinical abnormalities in the electrocardiogram (52). The advances in the use of the vectorcardiogram as a diagnostic tool is based on the approximation of the cardiac electrical generator as a current dipole (53). Similarly, patterns in the EEG have been modeled as surface reflections of underlying electrical sources (54).

The recent introduction of minimally invasive procedures for the treatment of diseases, including laparoscopic and thoracoscopic surgical procedures and radio-frequency ablation for cardiac arrhythmias, has intensified the interest of forward and inverse problems as a research area. For example, for radio-frequency ablation of ventricular tachycardia, it would be most helpful to localize, at least approximately, the origins of abnormal cardiac electrical activity from sensors either on the body surface or mounted on a catheter in the blood pool (55–57).

Computers have been used to model tissue at cellular and fiber levels of resolution. It is possible to simulate the propagation of electrical activity either with finite-state automata models (58) or by solving the differential equations that govern the current flow through the cell membrane (59–62). The electrophysiology of other organ systems has also been modeled effectively (63,64).

In addition to electrophysiological simulations, mechanical models have been applied to increase our understanding of the mechanical properties of soft tissue (65) and bone (66). Such models (Fig. 7) are important in simulating surgical procedures and implants (67) for training, planning, and evaluation of surgery.

VIRTUAL MEDICINE

Many of the computing techniques applied to medicine and medical sciences come together in the development of applications of virtual reality to medical practice (68,69). Virtual reality has been applied to surgery planning (70), physical medicine and rehabilitation (71), parkinsonism (72), and psychological disorders (73,74).

Computers have been used in a great many ways to assist in surgical procedures (70). Surgeons can be trained in surgical techniques by using advanced computer graphics and virtual reality methods (75,76); similar techniques can be used for surgical planning (77–79) and for improving the safety and efficacy of the surgical procedure. Computers are used during complex brain surgery as interactive tools for guiding and measuring the progress of the procedure, with the hope that resection of lesions could be performed with less damage to surrounding tissue (80). It is possible to use high-resolution graphics to traverse internal organs virtually, yielding much of the same information that is available from standard endoscopic techniques, as shown in the image in Fig. 8 acquired at the Mayo Clinic (68).

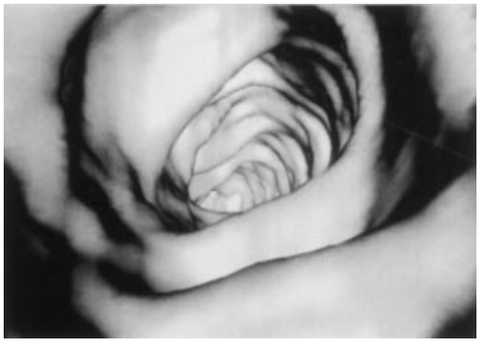

Figure 8. Virtual colonoscopy, with an internal view of the transverse colon. The image was acquired by a helical CT scan, segmented, and reconstructed. Virtual procedures can replace or augment actual endoscopic examinations, reducing or eliminating the attendant risk and discomfort. The image was acquired at the Mayo Clinic. Reprinted from Ref. 68, with permission. Copyright 1998, IEEE.

Computer technology has also made it possible for medical experts to use their knowledge at remote locations. This allows state-of-the-art medical diagnosis and treatment at sites where advanced technology would not normally be available (36). At another level, similar technologies have provided the necessary tools for minimally invasive surgery and microsurgery, using computer graphics and simulated tactile responses to extend the capabilities of the surgeon and to provide simulations for realistic rehearsals of the surgical experience (81,82).

The most sophisticated applications of computer graphics to remote and minimally invasive surgery have depended on the availability of high-resolution, high-quality graphical representations of the anatomy under treatment, either on an individualized basis (83) or as a global atlas of human anatomy (84).

REGULATION, RELIABILITY, AND PRIVACY

Computer software that controls devices used in the diagnosis and treatment of disease is of great interest to a regulatory agency of the US government, namely, the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). This agency maintains a World Wide Web site (http://www.fda.gov/cdrh/swpolpg.html) which provides guidance to device manufacturers in understanding regulatory policy enacted by the Federal Food, Drug and Cosmetic Act through a review of the FDA Software Policy Workshop. The CDRH also sponsors biannual workshops on software policy, the proceedings of which are included at this site. The Food, Drug and Cosmetic Act defines a medical device as any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or any other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . . or intended to affect the structure or any function of the body . . ." Software that is excepted from this includes general-purpose programs, such as spreadsheets, which are not intended solely for medical use, and a few other categories.

Independent of the regulatory issues, the design of medical software and systems requires the highest level of reliability and accessibility. The difficulty of developing robust computer programs and documenting their correctness are well known (85,86). The field of software engineering has been instrumental in providing tools for developing medical software that has the highest possible level of accuracy and reliability (87). Device manufacturers have recognized the importance and usefulness of software engineering principles in the design and implementation of control programs for their products.

Finally, ethical use of computer databases and the Internet for the transfer of medical information imposes a need for methods for strict privacy and security in data transmission. The rapid introduction of new technologies requires that the issues related to the sharing of patient information over openly accessible channels be continually evaluated and improved (88).

CARDIAC MAPPING

An area of medical practice and research that has benefited greatly by the use of computers and many computer-based techniques is cardiac mapping—that is, the use of technology to determine the path of electrical activity in the heart during normal and abnormal cardiac rhythms and to measure the effects of external stimuli and shocks that are applied therapeutically or as test perturbations. The activation sequence and response to interventions can be measured electrically (89,90) or optically (91,92). Electrical mapping is widely applied clinically to guide catheter-based or surgical interventions, and both technologies are important in investigating the mechanisms of electrophysiological phenomena. Both approaches are computer-intensive, requiring real time data acquisition, signal analysis, image acquisition, statistical analysis, data storage and manipulation, and visualization.

In electrical mapping, the first step is the transduction of the ionic currents in the cardiac tissue to electrical signals that can be input to the data acquisition system. The construction of electrodes is crucial to ensure that the appropriate variables are measured (93). Signals in optical mapping are generated by the application of fluorescent dyes that are sensitive to the electrical potential across the membranes of the cardiac cells. In either case, the waveforms are input to analog-to-digital converters.

In one implementation of an electrical cardiac mapping system (23), all of the parameters of the analog front end, including gains, frequency settings, and input range, are controlled by a series of microprocessors (94). The front-end processors assemble the data from 528 independent input channels into a data stream and send it to a data bus for recording on long- or short-term recording devices. Because of the complexity of the analog processing, the user interface has been designed to provide a great deal of direction and intuitive interaction with the investigators. Other microprocessors control stimulators (95) and associated investigational tools, such as defibrillators and waveform analyzers.

After the raw waveforms are acquired, digital signal processing algorithms are applied to them for several purposes. In some cases, the electrograms are analyzed to detect and locate in time local electrical activations, those events that represent the passage of an electrical wavefront in proximity to the electrode (96,97). The local activation times form the basis for other analysis programs. In other cases, the potential generated in the cardiac tissue from an external shock is measured in all electrodes (98) in order to understand the relationship between the electrical potential and gradient (99) distributions in the myocardium and the efficacy of the therapy. The results of a clinical mapping study are shown in Fig. 9. Figure 9(a) is a sequence of cardiac electrograms recorded using a commercial mapping system in a patient undergoing an electrophysiology study. The electrograms were recorded by a "halo" catheter placed in the right atrium, and they demonstrate the progression of an atrial flutter wavefront in a circular pattern. The activation is reentrant—that is, self-sustaining—and continually traverses the same anatomic pathway. Figure 9(b) is a plot of local activation times that were defined by the intrinsic deflection of the electrogram. Computer displays such as these guide the application of radio-frequency energy applied to the heart for ablation of arrhythmogenic tissue. Other useful parameters that emphasize other aspects of the electrophysiology can be derived from data such as these (100–103).

It is often necessary or, at least, helpful to know (1) the three-dimensional anatomy of the heart in which measure-

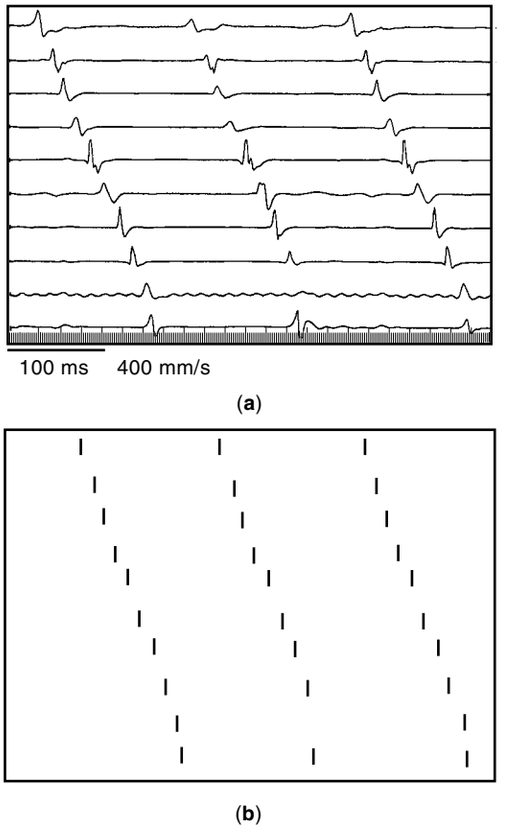

Figure 9. Results of a clinical electrical cardiac mapping study in a patient undergoing ablation of atrial flutter. (a) Electrograms recorded during the arrhythmia from a catheter inserted into the right atrium in a loop configuration. (b) Activations derived from the intrinsic deflections in the electrograms shown in panel a. The continuous nature of the activity demonstrates the reentrant mechanism around anatomical obstacles in the right atrium. Ablation can eliminate conductivity in part of the reentrant pathway, curing the atrial flutter.

ments are made and (2) the location of the electrodes used to make the measurements. These variables can then be used for further computations or to make the visualization of the results more compelling and useful (104). Imaging techniques as described above can be used for this purpose, allowing the application of standard image processing packages for better understanding of the electrophysiology (105). Image processing algorithms can also be used to improve our knowledge of the underlying pathology and its relation to abnormalities in electrical phenomena (35).

A traditional way of viewing activation sequences or other variables in the heart is through contour maps—that is, lines of equal values of activation time, potential, or other measured variable. The approach depends on whether the array of recording electrodes is two- or three-dimensional and whether the array is in a regular pattern or is irregularly spaced over the tissue. The variable of interest is typically interpolated over the region in which the measurements were made for more pleasing visual effects (106). Figure 10 is a simple isochronal map of the activation sequence beneath a rectangular array of electrodes on the outer, or epicardial, surface of the right ventricle of an experimental animal. Even though custom software is often used to produce contour maps (107), most commercial visualization packages have contour generation routines that are efficient and easy to use, especially for regular geometries, as indicated in Fig. 10.

With adequate processing, more complex displays can be produced. As discussed above, it can be most helpful to combine functional electrical information with anatomic data (49). Another approach is the animation of the activation sequence (108). By animating the color-coded values of time since last activation or potential or derivative of potential in each electrode as a function of time, the activation sequence can be effectively followed without explicitly defining times of local activation (Fig. 11) (109). If the electrodes are sufficiently close together, the displays can be produced without interpolation. Thus, animation has the potential of removing two important sources of ambiguity in cardiac mapping (110).

Traditionally, the interpretation of isochronal maps and activation sequences has been subjective and descriptive, with little basis for statistical comparisons between episodes of cardiac arrhythmias. Computer programs and algorithms have recently been developed which describe in quantitative terms the characteristics of supraventricular and ventricular flutter, tachycardia, and fibrillation. Some of them are aimed at inferring the level of organization of the arrhythmia, especially atrial and ventricular fibrillation (25,111). Others are designed to extract and identify wavefronts objectively as they course across the myocardial tissue and to quantitate their characteristics so that the effect of different experimental conditions and interventions can be compared in a rigorous and reproducible manner (112–114).

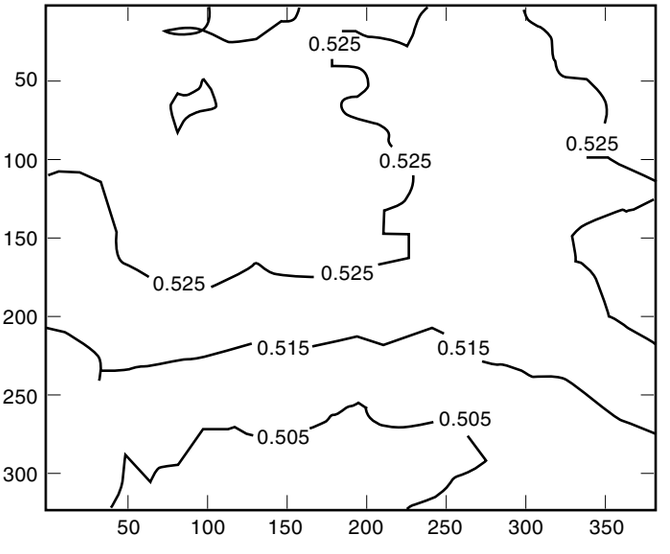

Figure 10. Isochronal map from activation times measured with a 21×24 rectangular array of electrodes placed on the right ventricular epicardium of a dog. The contours were interpolated to a 84×96 array, with linear interpolation. The lines represent times of equal activation, and they are spaced at 10 ms intervals. The labels of the isochrones are in seconds from an arbitrary reference time. The map was taken from a sinus beat and shows activation spreading from the apical region, at the bottom of the plot, to the base of the right ventricle. The loop in one of the isochrones demonstrates one of the problems with interpolation and isochrone production in data with noise.

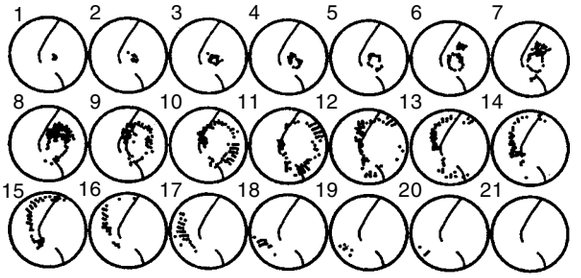

Figure 11. A sequence of frames from an animation of the activation sequence of the several cardiac cycles after an successful defibrillation shock. The circle represents an apical view of the heart, with the apex at the center and the base around the periphery. The data were recorded from a sock containing 510 electrodes which was pulled over the ventricular epicardium. The left anterior descending coronary artery is the line from the top of the circle to near the center and the posterior descending coronary artery is the line at the bottom. Each dot represents a time at which the electrogram recorded by the corresponding electrode is "active," meaning that the absolute value of the derivative of the electrogram exceeded a preselected threshold. The earliest postshock activation is in the apical region of the left ventricle. A secondary early site appears in panel 7. The two wavefronts merge, and then they spread to the right ventricle. Even though the data were sampled at 2 kHz, the sequential displays are at 5 ms intervals. Animation of electrograms in this manner can provide information about the activation sequence without explicitly defining times of local activation in each electrogram. Reprinted from 109, with permission.

CONCLUSION

Computers are used in almost every aspect of clinical medicine and biomedical research. They are indispensable in advanced devices and instrumentation. They are widely used for the collection and analysis of demographic and clinical data which provide a basis for the improved understanding of the causes and epidemiologies of disease. They can be very effectively used for the training and accreditation of physicians and other health care providers. While obviously no substitute for human clinical and scientific judgement, computers have assumed a critical role as facilitators of diagnostic and therapeutic procedures. As the inevitable progress in computer software and hardware occurs, medical professionals will become more dependent on them. There will be continuing improvement in our understanding of methods for increased reliability and safety of computer-based devices and equipment, and regulatory agencies will develop procedures for evaluating these resources routinely and objectively. Advanced imaging technologies, higher performance graphics hardware and software, and new surgical techniques will expand the use of microsurgery and remotely applied surgical and invasive procedures. These prospects will depend on investigators in computer science, biomedical and software engineering, clinical practice, and physiology, but the computer has the potential to be a positive force in improving health care delivery while decreasing the financial burden of the health care system on society.

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