

Advances in Biomedical Engineering

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BIOMEDICAL ENGINEERING IS broadly defined as the application of engineering principles to problems in clinical medicine and surgery. The origins of biomedical engineering are often linked to the pioneering electrophysiology studies of Galvani and Volta more than 200 years ago.¹ During the first half of the 20th century, the electrical properties of tissues and cells continued to be a primary focus of biomedical engineering. Emerging interests in the health effects of ionizing radiation between World Wars I and II laid the groundwork for current radiation therapy. It was not until the 1960s and 1970s, however, that an explosion in multidisciplinary research, combining mechanical, chemical, and electrical engineering with physiology and medicine paved the way for dramatic advances in modern health care based on breakthrough discoveries in biomedical engineering.²

Clinical and Research Advances

The most visible contributions of biomedical engineering to clinical practice involve instrumentation for diagnosis, therapy, and rehabilitation.³ A revolution in disease diagnosis began in the 1970s with the introduction of computed tomography, magnetic resonance imaging, and ultrasonic imaging.⁴⁻⁸ Computed tomographic scanning, developed at EMI Research Labs (Hayes, Middlesex, England) (funded in part by the success of EMI's Beatles records) provided the first high-

The most visible contributions of biomedical engineering to clinical practice involve instrumentation for diagnosis, therapy, and rehabilitation. Cell and tissue engineering also have emerged as clinical realities. In the next 25 years, advances in electronics, optics, materials, and miniaturization will accelerate development of more sophisticated devices for diagnosis and therapy, such as imaging and virtual surgery. The emerging new field of bioengineering—engineering based in the science of molecular cell biology—will greatly expand the scope of biomedical engineering to tackle challenges in molecular and genomic medicine.

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quality, cross-sectional images of the body.⁹ Magnetic resonance imaging further revolutionized imaging of soft tissues, enabling both the imaging of static structures and dynamic function, such as blood flow and metabolism. Open magnetic resonance imaging scanners are used in operating rooms to guide biopsies and stereotactic surgery.⁷ Ultrasound also affords soft-tissue imaging, with lower resolution but at reduced cost and thus increased accessibility compared with magnetic resonance imaging.⁸

The development of these imaging modalities has been accompanied by exciting advances in 3-dimensional image reconstruction, quantitative image analysis, and image enhancement—advances that were made possible by improved computational power and algorithms. The development in the 1980s of the noninvasive pulse oximeter was a significant advance in intraoperative monitoring and postsurgical care.¹⁰

Biomedical engineering has also been responsible for the development of new therapeutic devices. The cochlear implant, for example, has now been used

in 20000 of the 1 to 2 million deaf individuals in the United States, many showing dramatic improvement.¹¹ Sound is decomposed into critical frequency bands and signals are delivered electronically to auditory neurons via an array of electrodes.

Cardiovascular therapy has been similarly changed by the introduction of lifesaving implantable defibrillators (1980s),¹² and ventricular-assist and catheter-based ablation devices. In addition, vascular stent technology for the treatment of aneurysms, peripheral vascular disease, and coronary artery disease has made it possible for a minimally invasive procedure to replace major surgery.¹³ The shift toward minimally invasive surgery, driven by development of miniaturized cameras, laser guides, and surgical tools, has had

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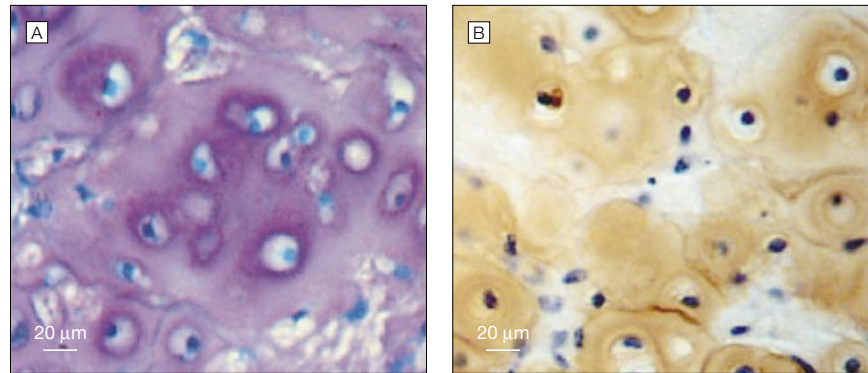
a profound effect in reducing morbidity and mortality, and enabling faster rehabilitation.

Cell and tissue engineering also have emerged as clinical realities. Products for skin replacement are in clinical use^{14,15} and progress has been made in developing technologies for repair of cartilage (FIGURE 1),^{16,17} bone, liver, kidney, skeletal muscle, blood vessels, the nervous system, and urological disorders.¹⁵ The discovery that mechanical forces are potent regulators of cell-mediated growth, degradation, and repair of musculoskeletal^{17,18} and cardiovascular¹⁹ tissues presents a major challenge and elucidation of the mechanisms involved in mechanical signaling and cellular mechanotransduction will be needed to develop new therapies for a true understanding of osteoarthritis, osteoporosis, and atherosclerosis, and for the development of tissue engineering therapies.

At the same time, the field of biomedical engineering is undergoing a major ideological change. The fusion of engineering with molecular cell biology is pushing the evolution of a new engineering discipline termed *bioengineering* to tackle the challenges of molecular and genomic medicine. In much the same way that the iron lung (an engineered device) was rendered obsolete by the polio vaccine (molecular medicine), many of the device-based and instrumentation-based therapies in clinical use today will likely be replaced by molecular- and cellular-based therapies during the next 25 years. Realization of these therapies will require major contributions from bioengineering.

Arguably the most well-recognized contributions of bioengineering have been at the level of obtaining molecular information—techniques that make it possible at the research, development, and even clinical levels to manipulate, sequence, reconstruct, and model proteins and nucleic acids, such as polymerase chain reaction, DNA sequencing, molecular modeling, and bioinformatics. On this molecular level, the most stunning successes in terms of

Figure 1. Tissue Engineering of Cartilage



After 2 weeks of culture, cartilage cells seeded onto a scaffold have synthesized a biomechanically stable cartilage-like extracellular matrix¹⁷ containing phenotypically specific aggregating proteoglycans (A, toluidine blue stain) and type II collagen fibrils (B, immunohistochemical stain). The scaffold material is a recently discovered self-assembling gel¹⁶ made from repeating sequences of the amino acids lysine, leucine, and aspartic acid. This biomaterial can be used simultaneously as a cell-supporting structure for gene delivery to the cells.

data acquisition are clearly in genomics. For example, DNA microarrays, involving analysis of expression profiles of thousands of genes simultaneously, are being applied for biomedical research and pharmaceutical development.²⁰

Yet many engineering challenges remain to be solved before the power of DNA microarray analysis is optimal.²¹⁻²³ Many drugs developed through molecular-level assays prove to be ineffective, and bioengineering analysis is beginning to point the way to better drug design and better drug testing. Most pressing for genomics is the lack of appropriate computational tools for the analysis and interpretation of expression profile data (ie, bioinformatics). Current tools consist largely of algorithms that group genes according to shared expression patterns.²¹ In addition, hybridization is not always sufficiently reliable or sensitive; there is a great need for better design of hybridization chips as well as algorithms to account for data imperfections.²² The cellular messenger RNA levels measured by microarray analysis do not strongly correlate with corresponding protein levels, further clouding the interpretation of microarray data.²³

Proteins are the molecules that regulate metabolic processes and signaling pathways and most drugs target pro-

teins and protein-protein interactions.²⁴ Thus, analysis of cellular protein profiles (proteomics) may be particularly valuable in drug discovery and analysis of disease states. Proteomics is less advanced than genomics because of the greater complexity of protein, but advances in mass spectrometry analysis of proteins are causing a revolution in proteomics.²⁴ Proteomic analysis shares some of the same challenges as genomic analysis in terms of improving sample preparation, throughput, reliability, and means of analyzing massive data sets.

Engineering analysis often entails building complex systems models by integrating detailed mathematical models of the physical and kinetic properties of the component parts. Such analysis entails making assumptions about the nature of missing information to build predictive models of the system as a whole when the properties of 1 component are altered. Even though the individual processes contributing to performance may be poorly understood, models of biological systems contribute to application of the biological information, such as improved, targeted drug therapies, in the absence of complete data on cellular genes and proteins.

Insights gained from such complex models are often both nonintuitive and

Recent Advances in Biomedical Engineering	
Diagnostics	
Imaging Modalities	Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography, and Ultrasound; Nuclear Image Reconstruction
Monitoring	Sensors and Transducers (Intensive Care Unit; eg, Pulse Oximeter)
Instruments and Devices	Clinical Laboratory
Therapeutics	
Sensory/Motor	Intraocular Lens and Cochlear Implants
	Implantable Nerve Stimulators
Cardiovascular	Defibrillators and Pacemakers (Implantable and Programmable)
	Ventricular Assist Devices
	Catheter-Based Ablation and Balloon Pumps
	Stents
Renal/Respiratory	Kidney Dialysis
	Artificial Lungs and Blood Gas Exchange Devices
Tissue/Organ Failure	Organ Transplantation; New Materials
	Kidney Dialysis
	Prostheses and Implants (eg, Total Joints)
Tissue Engineering	Artificial Skin (First Product); Progress in Cartilage Repair, Bone, Liver, Kidney, Skeletal Muscle, and the Nervous System
Biotechnology and Biomaterials	Monoclonal Antibodies and Protein Engineering
	Vaccines; Gene Therapy
	Natural and Synthetic Materials; Biodegradables
Surgery and Rehabilitation	
Devices and Procedures	Minimally Invasive Surgery (eg, Arthroscopy, Laparoscopy, Endoscopy)
	Prostheses and Orthotics; Sensory Augmentation and Substitution; New Materials; Wheelchair Mobility

valuable. For example, high-throughput screening assays to identify compounds for potential drug develop-

ment typically identify compounds that bind with high affinity to a receptor. Models of the cellular pharmacology of

receptor-ligand interactions, which integrate separate mathematical descriptions of ligand binding and release, receptor activation and desensitization, and receptor internalization, recycling, and degradation indicate that classic strategies based solely on high-affinity equilibrium binding can fail to predict drug candidates—for some receptors, lower affinity compounds may be more effective.

For example, transforming growth factor α is more potent than epidermal growth factor in stimulating cell growth, even though transforming growth factor α has a lower binding affinity than epidermal growth factor to their common cell surface receptor. Surprisingly, a detailed cellular bioengineering model shows that lower affinity binding, particularly at the pH of the endosome, leads to less degradation both of receptor and ligand and increases receptor recycling. More important, a ligand designed via molecular engineering (ie, rational design of protein-protein interactions), which incorporates a single amino acid change resulting in a binding affinity below that of epidermal growth factor or transforming growth factor α , is a more potent ligand.²⁵

This type of cell-level analysis, based on defining interlinked dynamic processes, is now being applied to engineer drugs that affect other receptor pathways, such as interleukin 2²⁵ and G-protein-coupled receptors.²⁶ The potential implications for the drug discovery process are profound. Such analyses and design principles are also being applied to tailor vectors for gene therapy to increase specificity and efficiency of transfer and to design synthetic molecules to control cell behaviors in tissue engineering.²⁶

Cell- and molecular-level models are the building blocks for development of mathematical models of entire systems. The advent of powerful computers and graphical interfaces has made possible the development of complex models that span levels from genes to organ systems, including feedback responses across all these levels.²⁸ Such

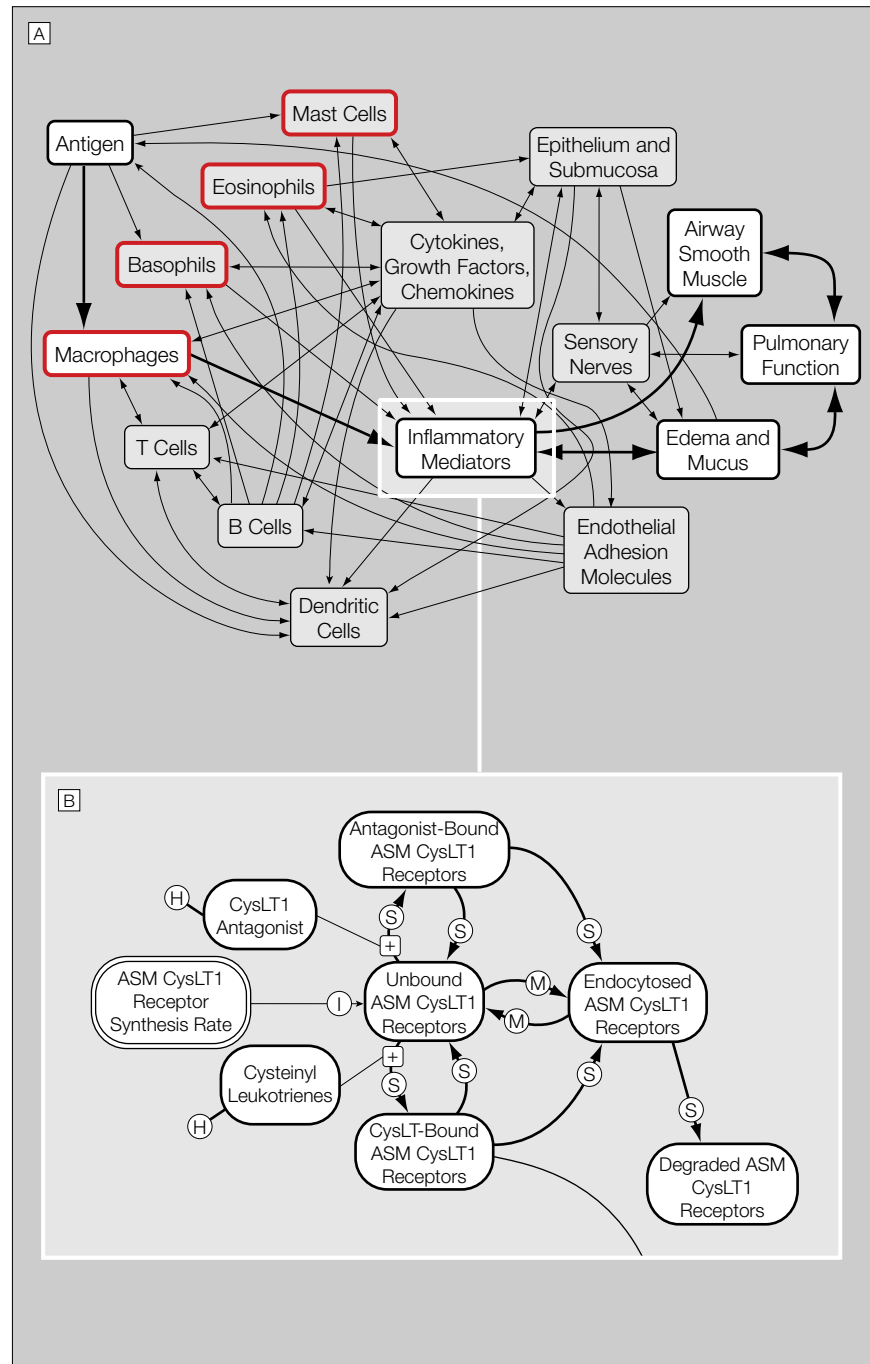
models make it possible to predict how a complex, nonlinear, and expensive experimental system (eg, a nonhuman primate or a human) will respond based on input from cell culture or biochemical assays. In the next 25 years, several large-scale systems modeling efforts at the academic level (eg, the Physiome Project, www.physiome.org), and at the commercial level (eg, Physiome Sciences [Princeton, NJ] and Entelos Inc [Menlo Park, Calif]) will become available. For example, a simulation of asthma (FIGURE 2) that relates dynamic changes at the biochemical level (eg, leukotriene production) to functional outcomes (eg, the degree of compromised breathing in a patient with asthma)²⁸ illustrates the utility of this approach.

Forecast for Research Advances

In the next 25 years, advances in electronics, optics, materials, and miniaturization will push development of more sophisticated devices for diagnosis and therapy, such as imaging and virtual surgery. The accelerating pace of development of bioMEMS (biomicroelectromechanical systems, integrating electrical, mechanical, and optical systems on a micro scale) and microfluidic (incorporating microlevel fluid pumping, mixing, and reaction circuits) systems, combined with bioinformatics, will likely give rise to a new era of “lab on a chip” diagnostics, enabling routine and sensitive analysis of thousands of molecules simultaneously from a single sample. Such analysis might be done on a yearly basis in the way cholesterol screening is now done.

A potentially even greater impact of bioengineering will result from the increased ability to incorporate molecular-level information into complex models. The result will be a revolution in diagnosis and treatment of diseases ranging from osteoarthritis to Alzheimer disease. Either by looking for single-signature molecules (eg, cancer antigens) or by using appropriate algorithms to derive relationships between many interacting molecules, early prediction of onset of disease may be

Figure 2. Systems Model of Asthma Physiology



A, Overall systems diagram shows the complex interactions between multiple classes of cells and mediators that affect the response of a patient with asthma to an antigen trigger. The simulation quantitatively relates dynamic changes at the biochemical level to functional outcomes in the patient allowing scientists to predict how small-scale changes, such as in leukotriene production by macrophages (bold pathway), might affect the pulmonary function of a patient with asthma.²⁸ B, Molecular-level detail from the large-scale systems model shows the pathways modulating the effect of cysteinyl leukotriene action on airway smooth muscle (ASM) via cysteinyl leukotriene receptor subtype 1 (CysLT1). Leukotrienes are produced by several cells of the immune system (bold red rectangles in panel A). The nodes (rounded rectangles) and arrows contain specific mathematical functions that describe the relationships among system components and enable simulation of the biological system dynamics. Arrow labels categorize actions: H indicates half-life; S, change of state; M, moves; I, increases; plus sign (+), stimulates. Reproduced from Entelos Asthma PhysiLab by permission from Entelos, Inc ©2001 Entelos, Inc.

Research Opportunities and Forecast: Biomedical Engineering	
Areas of Research Opportunity	Forecast
Molecular Engineering Rational Alteration of Molecular Structure Using Thermodynamic, Kinetic, and Mass Transfer Analysis to Improve Selectivity, Cellular Potency, Distribution in Target Tissue and Overall Pharmacology; May Involve Combinatorial Production With Rational Screening Assay	Tailored Monoclonal Antibodies and Cytokines for Inflammatory Diseases, Cancer Therapy, Targeted Gene Delivery, and Diagnostics
	Nonviral and Hybrid Viral Gene Therapy Vectors
	Assays for Development of Drugs That Target Protein-Protein Interactions
	Biomaterials to Control Cell Selection and Cell Proliferation, Migration, and Differentiation for Tissue Engineering and Integration of Devices (Such as Neural Probes) Into Tissues
Cell Engineering Design of Cellular Microenvironments In Vitro to Control Cell Proliferation and Differentiation Using Quantitative Models of Cellular Response to Multiple Inputs From Matrix and Cytokines; Systematic Alteration of Cellular Properties (eg, Adhesion Receptor Expression) to Control Cell Behavior In Vivo	Selection, Culture, and Propagation of Stem Cells
	Genetic Transfection
	In Vitro Cell-Based Assays for Drug Development
	Improved Stem-Cell Homing
	Engineering and Delivery of Cells for Local Immune Therapy (eg, Delivery of Cytokine to Tumors)
	Optimization of Product Production in Large-Scale Culture of Cells to Lower Therapeutic Protein Production Costs
Tissue Engineering Construction of 3-Dimensional Tissue, Usually Using a Porous Synthetic Scaffold to Direct Growth of Tissue Into Appropriate Structure or to Protect Tissue Immunologically, by Transplanting Cells From the Patient or Donor, or Directing New Growth From Surrounding Healthy Tissue	Regeneration of Damaged or Diseased Connective Tissue (Bone, Tendon, Cartilage)
	Replacement of Metabolic Tissues (Islets, Liver)
	In Vitro Physiological Models for Drug Development and Study of Disease Processes to Ultimately Replace Animal Studies
BioMEMS and Microfluidics Biomicroelectromechanical Systems (BioMEMS) Use Integrated, Electrical, Mechanical, Optical, and Fluidic Systems on a Microscale or Milliscale, Typically Microfabricated on a Silicon Chip	Rapid and Sensitive Molecular, Cellular, and Tissue-Based Assays for Laboratory and Home Diagnostics: "Lab on a Chip"
	Synthesis of New Drug Compounds and High Throughput Drug Screening Assays
	Manipulations of Single Cells or Small-Cell Populations (eg, for In Vitro Fertilization); Biochemical and Bioassays (eg, Polymerase Chain Reaction, Electrophoresis)
Virtual Surgery and Nanoinstrumentation Simulated Environment Using Interactive Imaging That Enables the User to Remotely Experience Events 3-Dimensionally	Surgical Training and Planning and Remote Surgical Procedures Using Interactive Telecommunications and Virtual Reality
	Endoscopic Applications Using State-of-the-Art Nanoelectromechanical Tools and Devices
Imaging Visualization of Organs, Tissues, and Physiological Processes by X-ray, Nuclear, Magnetic Resonance Imaging, Positron Emission Tomography, and Optical Modalities	Advances in Resolution and Bandwidth of Magnetic Resonance Imaging and Ultrasound for Real-Time Diagnostics
	New Developments in Optical Imaging (eg, Optical Coherence Tomography)
Bioinformatics Databases, Algorithms, and Computational Tools to Enable Analysis and Interpretation of Complex Information	Analyzing and Interpreting Massive Data Sets From Genomic and Proteomic Assays

possible. For example, osteoarthritis might be detected just when cartilage degradation begins and before damage is irreversible; Alzheimer disease might be detected in early adulthood when it is believed lesions might first form and before cognitive decline. In

each case, new drugs developed with the aid of molecular and cellular engineering will likely be available to combat disease progression. For osteoarthritis, these advances would obviate the need for joint replacement surgery or even for cell transplantation. For Alz-

heimer disease, which lacks current therapeutic options, the impact of bioengineering will be extraordinary.

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