

CHAPTER 1

OVERVIEW

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Abstract

As indicated in the Preface, the theme of this book is *Integrative Bioengineering*, which brings together the fundamental concepts and techniques in engineering and biomedical sciences and demonstrates their interplays. It is organized in a cohesive manner to facilitate learning and to stimulate innovation. There are eight sections that are composed of 30 chapters. Section I is introductory in nature, and it is followed by Secs. II to IV that cover the bioengineering of several organ systems, with a close relation to physiology, i.e. Cardiovascular Bioengineering, Blood Cell Bioengineering, and Respiratory-Renal Bioengineering. Sections V to VII present three new areas of developments in bioengineering, viz. Tissue Engineering & Regenerative Medicine, Nanoscience & Nanotechnology, and Genomic Engineering & Systems Biology. The last section (VIII) addresses the important socio-economical aspects of bioengineering.

Section I on Introductory Chapters provides an Overview of the book in this Chapter 1 and Perspectives of Biomechanics in Chapter 2.

Chapter 2. *Perspectives of Biomechanics*, by Y. C. Fung and Wei Huang: Biomechanics, which is mechanics applied to biology, covers a wide territory. In this chapter, the use of biomechanics in bioengineering is illustrated with several examples on tissue remodeling in blood vessels. These examples include the determination of zero stress state of a blood vessel from its opening angle, which changes after hypertension and following tissue remodeling, the usage of the intrinsic modes approach for the analysis continuous, the elucidation of the dynamics of tissue remodeling from long-term blood pressure recording, and the correlation of gene expression and physiological changes to understand how forces trigger gene actions for tissue remodeling. The overall objective is to demonstrate how theory and experiment can be coupled, and how design and science are linked in biomechanics.

Section II on Cardiovascular Bioengineering is composed of five chapters (3 to 7), which present the functions of the heart and blood vessels across the entire biological hierarchy, from molecules/cells to tissues/organs, as well as the cardiovascular system as a whole, under normal conditions and in disease states. These chapters illustrate how bioengineering approaches are used to study cardiovascular physiology and pathophysiology in health and disease.

Chapter 3. *Cardiac Electromechanics in the Healthy Heart*, by Roy Kerckhoffs and Andrew McCulloch. This chapter provides a multi-scale description of cardiac structure and electrical and mechanical functions, from the organ level to tissue and cell scales. Electrical function in the heart is intimately linked to mechanical function. Muscle contraction at the cellular level is triggered by electrical activity via the flux of calcium ions, while cell electrophysiology is modified by feedback from mechanical alterations (mechano-electric feedback). These electromechanical interactions have important medical implications, e.g. their roles in regional wall remodeling induced by clinical therapy such as chronic pacing and cardiac resynchronization therapy. Examples are given to illustrate the iterative interactions between bioengineering experiments and simulations that help in understanding cardiac function.

Chapter 4. *Cardiac Biomechanics and Disease*, by Jeffrey H. Omens: Biomechanics plays a central role in research on cardiac structure and function, and diseases of the heart are often the direct consequence of impaired mechanics. There is a need to understand the structure and function of the heart in quantifying cardiac function via experimental procedures at multi-scales in health and disease. Determinations of cardiac function range from the measurement of cardiac output in the intact system to experimental procedures on cardiac muscle cells, as well as roles of individual proteins within the cells and the extracellular matrix. It is important to determine how the heart responds to external loads and whether it can transduce the mechanical signals to provide adequate compensatory growth; the inadequacy of these responses can lead to failure of the mechanical pump.

Chapter 5. *Bioengineering Solutions for the Treatment of Heart Failure*, by John T. Watson and Shu Chien. In heart failure, the heart cannot pump a sufficient blood flow to meet the body's metabolic requirements; it can result from coronary artery disease, high blood pressure, diabetes, and several other conditions. The incidence of heart failure has steadily increased over the last 50 years and presents a major public health problem that needs a bioengineering solution. Design principles are presented for mechanical circulatory support systems, including ventricular assist devices and heart replacements or total artificial hearts. These systems have provided safe and successful alternatives in treatment for cardiac transplantation in end-stage heart failure patients. This is still a nascent field that will benefit greatly from advances in bioengineering and related fields.

Chapter 6. *Molecular Basis of Modulation of Vascular Functions by Mechanical Forces*, by Shu Chien: Mechanical forces such as shear stress can modulate cellular functions. This chapter discusses the participation of a multitude of mechano-sensors in

initiating mechanotransduction by activating signaling pathways to modulate gene and protein expressions in endothelial cells, and hence their functions. Sustained laminar shear stress with a definite direction, as seen in straight part of the aorta, is protective against atherosclerosis by down-regulating the expression of chemotactic and up-regulating growth-arrest molecules. In contrast, the disturbed flow (without clear direction) observed at branch points up-regulates molecules that enhance monocyte entry, endothelial turnover, and lipid permeability, and are hence atherogenic. Coupling of mechanics and biology helps to elucidate vascular functions in health and disease.

Chapter 7. *Autoregulation of Blood Flow*, by Paul C. Johnson: Autoregulation is the tendency for blood flow to remain constant in an organ during changes in arterial pressure. It results from local regulatory mechanisms in the organ and is independent of the control by the central nervous system. This chapter examines the evidence for and against the two possible explanations, i.e. the metabolic hypothesis (with metabolic mediators as the stimulus) and the myogenic hypotheses (with intravascular pressure as the stimulus). Autoregulation may be important in clinical situations such as atherosclerosis and hemorrhage. Reviewing the development of experimental evidence for the two hypotheses provides insight to the manner in which concepts arise and are tested experimentally.

Section III on Blood Cell Bioengineering is composed of three chapters (8 to 10), which present the molecular basis of cell and membrane mechanics (with a focus on the red blood cell membrane and its role in blood rheology), the role of white blood cell activation and inflammation in the induction of cardiovascular diseases, and the design of blood substitutes based on bioengineering considerations of oxygen delivery and rheology of blood flow.

Chapter 8. *Molecular Basis of Cell and Membrane Mechanics*, by Lanping Amy Sung: This chapter discusses the interrelation and integration between biomechanics and molecular biology, as exemplified by the author's research on the red blood cell (RBC) membrane. The interdisciplinary work involves the cloning of cDNAs that encode RBC membrane skeletal proteins, characterization of the genomic organization, creation of gene-knockout mouse model by disrupting a target gene in an embryonic stem cell, expression of recombinant proteins and mapping their binding sites, mechanical testing of genetically engineered erythrocytes, construction of the first 3-D model for a junction complex, and establishment of the 3-D nano-mechanics of RBC membrane skeleton. This chapter provides a valuable example for the new generation of bioengineers on how to combine engineering principles and techniques with molecular genetics.

Chapter 9. *The Auto-Digestion Hypothesis for Cell Activation in the Circulation*, by Geert W. Schmid-Schönbein. Studies on a variety of acute and chronic disease conditions have identified a common feature in terms of *inflammation*, which can be triggered by many abnormal states to lead to tissue injury. Inflammation can be detected by the presence of enhanced concentrations of certain proteins in the plasma. There is

evidence that the pancreas can release a digestive enzyme into the blood under low-flow condition to activate white blood cells in the blood to cause inflammation. The study of white blood cell activation and inflammation may serve as a key entry point to develop a systematic model of cardiovascular disease. This chapter provides an example of using rigorous engineering analysis to develop novel medical intervention.

Chapter 10. *Blood Substitutes and the Design of Oxygen Non-carrying and Carrying Fluids*, by Marcos Intaglietta. Analysis of oxygen transport at the level of microscopic blood vessels has resulted in the development of blood substitutes with novel properties different from blood, including a high oxygen affinity that allows the targeting of oxygen delivery to regions with low pO_2 and a high viscosity that insures the maintenance of functional capillary density in extreme anemia. The design of the blood substitutes is based on the conjugation of polyethylene glycol with molecular hemoglobin. These novel substitutes have been shown to be effective in treating conditions such as hemorrhage and extreme hemodilution, thus providing a realistic re-deployment of existing resources of human blood.

Section IV on Respiratory-Renal Bioengineering is composed of three chapters (11 to 13), which present the bioengineering approaches to study the pulmonary circulation, gas exchange in the lung, and functions of the kidney. These chapters emphasize the importance of biological structure, biomechanics, and transport processes in the regulation of pulmonary and renal functions in health and disease.

Chapter 11. *Analysis of Human Pulmonary Circulation with a Bioengineering Approach*, by Wei Huang, Michael R. T. Yen, and Qinlian Zhou: This chapter presents a bioengineering approach to study human pulmonary circulation based on the principles of continuum mechanics in conjunction with detailed measurements of pulmonary vascular geometry, vascular elasticity, and blood rheology. Experimental data are used to construct a mathematical model of pulsatile flow in the human lung. Input impedance of every order of pulmonary blood vessels is calculated under physiological condition, and pressure-flow relation of the whole lung is predicted theoretically. The influence of variations in vessel geometry and elasticity on impedance spectra is analyzed. The goal is to understand the detailed pulmonary blood pressure-flow relationship in the human lung for clinical application.

Chapter 12. *Pulmonary Gas Exchange*, by Peter D. Wagner: This chapter discusses a linked series of transport functions that employ both convective and diffusive movements of gases. Ventilation brings O_2 from the air to the 300 million alveoli during inspiration by convection. Gas diffusion in the alveoli leads to the elimination of CO_2 during expiration. Pulmonary blood flow, again being convective, moves the blood out of the alveolar capillaries and back to the left heart for distribution to the tissues. These three transport functions (ventilation, diffusion and perfusion) can be modeled mathematically with remarkable accuracy using simple mass conservation principles. Such interdisciplinary approaches illustrate the application of engineering principles of transport process for the understanding of respiratory functions.

Chapter 13. *Engineering Approaches to Understanding the Kidney*, by Scott C. Thomson. Engineering models have been essential for the understanding of the various functions of the kidney, including the mechanisms, control and regulation of glomerular filtration, tubular reabsorption, as well as the elaboration of a concentrated urine. Following a brief overview, this chapter discusses how engineering approaches can be used to understand these kidney functions and how they are stabilized by the internal negative feedback mechanisms. The application of the core attributes of engineering, viz. imagination, judgment, and mathematical reasoning, will remain essential to the comprehension of kidney physiology, including the explanation of the properties and functions that arise from the interacting parts in this complex organ.

Section V on Tissue Engineering and Regenerative Medicine is composed of five chapters (14 to 18), which present research and development of skeletal muscle tissue engineering, articular cartilage biomechanics, *in vivo* force-sensing knee prosthesis, implantable glucose sensors for diabetes, and stem cells in regenerative medicine. These chapters illustrate how engineering principles and techniques can be applied to the regeneration of tissues and organs, including the use of stem cells.

Chapter 14. *Skeletal Muscle Tissue Engineering*, by Richard L. Lieber and Samuel R. Ward: Skeletal muscle represents a classic example of structure-function relationship in the biological system. Skeletal muscle anatomy can be determined by using a combination of direct tissue dissection and magnetic resonance imaging (MRI). A major determinant of whole muscle force is the skeletal muscle architecture, including the orientation and number of fibers within the muscle. Within each muscle fiber, the arrangement of the sarcomeres is a major determinant of the muscle fiber force generated. The sarcomeres are sensitive to length and velocity. Virtually every aspect of skeletal muscle architecture and function can be studied using the modern tools of bioengineering that include imaging, mechanics, molecular biology, cell biology and bioinformatics.

Chapter 15. *Multi-Scale Biomechanics of Articular Cartilage*, by Won C. Bae and Robert L. Sah. Articular cartilage is the connective tissue that covers the ends of bones in the body, bearing and transmitting load while allowing low-friction and low-wear joint articulation. The biomechanical functions of articular cartilage have been examined at multiple length scales, ranging from intact joints to cellular and molecular components. This chapter provides an introduction to (1) the composition, structure, and function of articular cartilage, (2) biomechanical tests of articular cartilage, and (3) mathematical analysis of tissue deformation and strain. The knowledge gained from the multi-scale biomechanical studies facilitates the understanding of cartilage function in growth, aging, health and disease.

Chapter 16. *Design and Development of an In Vivo Force-Sensing Knee Prosthesis*, by Darryl L. D'Lima and Peter C. Y. Chen: A total knee replacement tibial tray component with four embedded force transducers and a telemetry system has been developed to measure directly tibiofemoral compressive forces *in vivo*. After extensive laboratory

testing to determine performance, accuracy and safety, trial surgical implantation has been performed to demonstrate feasibility and to assess the utility of the prosthesis as a dynamic ligament-balancing device for proper alignment and success of the operation. Knee forces are monitored during recovery and rehabilitation, as well as in daily living and exercise. These measurements are supplemented by video motion analysis, electromyography, and ground reaction force measurement to provide the information needed for the orthopedic scientific community to improve knee prosthesis design.

Chapter 17. *The Implantable Glucose Sensor in Diabetes: A Bioengineering Case Study*, by David A. Gough: Regulation of blood glucose by the body is a fundamentally important process that is impaired in diabetes, which has become increasing more prevalent as a serious health problem. Since the basis of all therapies for diabetes is the restoration of normal blood glucose control, glucose monitoring is of central importance. This chapter focuses on the recent advances made in the author's laboratory to develop implantable glucose sensor technology and the efforts to close the loop to maintain glucose homeostasis. These developments provide an excellent example for the combination of engineering principles and technology with biomedical experimentation in solving an important health problem.

Chapter 18. *Stem Cells in Regenerative Medicine*, by Shu Chien and Larry Goldstein: Stem cells can either self-renew for long periods without differentiation or can become differentiated under specific conditions into specialized cells. They have great potential to treat disease someday by regenerating the dysfunctional cells or by providing novel ways to develop either drugs or other therapies. Embryonic stem cells are pluripotent in that they can differentiate into all types of cells in any organ/tissue. Adult stem cells are multipotent in that they differentiate only into the types of cells that exist in the organ/tissue in which they reside. There is the possibility that adult stem cells may become pluripotent and differentiate into cells of other organs/tissues. Bioengineers can play a significant role in fostering the advance of stem cell research and its eventual clinical applications.

Section VI on Nanoscience and Nanotechnology is composed of four chapters (19 to 22), which present the new developments in this cutting-edge field, including the engineering of compounds targeting to vascular zip codes, use of nanoengineering approaches to study and repair the central nervous system, utilization of cellular biophotonics to solve bioengineering and medical problems, and application of microelectronic arrays for DNA hybridization diagnostics and self-assembly nanofabrication. The application of these novel developments has important medical implications in improving the diagnosis and therapy of a variety of diseases.

Chapter 19. *Engineering Compounds Targeted to Vascular Zip Codes*, by Erkki Ruoslahti: The blood vessels in different tissues carry specific molecular markers. Various disease processes, such as cancer, inflammation or atherosclerosis, express their own molecular markers on the vasculature to create a "zip code" system of vascular addresses. The vascular addresses for tissues and disease processes reside in the

endothelium lining the blood vessels, and are thus readily accessible from the blood stream. The screening of phage-displayed peptide libraries *in vivo* has been an effective way of identifying vascular zip codes. Targeting a drug to these addresses can enhance the efficacy of the drug while reducing its side effects. The greatest potential of the vascular targeting technology may be the construction of smart nanodevices.

Chapter 20. *The Structure of the Central Nervous System and Nanoengineering Approaches for Studying and Repairing It*, by Gabriel A. Silva: Nanotechnologies involve materials and devices with an engineered functional organization at the nanometer scale. Applications of nanotechnology to biology and physiology provide targeted interactions at a fundamental molecular level. In neuroscience, this entails specific interactions with neurons and glial cells. Examples include technologies designed with improved interactions with neural cells, advanced molecular imaging technologies, applications of materials and hybrid molecules for neural regeneration and neuroprotection, and targeted delivery of drugs and small molecules across the blood-brain barrier.

Chapter 21. *Cellular Biophotonics: Laser Scissors (Ablation)*, by Michael W. Berns: This chapter examines the use of light (photons) at tissue and cellular levels with a focus on the understanding and application of light to solve bioengineering and medical problems. The presentations in this chapter include the mechanisms of photon interaction at the tissue and cellular levels, the use of light and light-sensitive photochemical agents for the diagnosis and treatment of cancer, and the use of a laser microbeam at cellular and subcellular levels. Also discussed are the use of laser microbeam to manipulate the organelles of dividing cells, the use of GFP gene-fusion proteins in facilitating visualization and targeting of subcellular structures, and the combined use of cell tracking and robotics in developing an internet-based laser microscope.

Chapter 22. *Microelectronic Arrays: Applications from DNA Hybridization Diagnostics to Directed Self-Assembly Nanofabrication*, by Michael J. Heller and Dietrich Dehlinger: This chapter describes the microelectronic array devices that have been developed for DNA hybridization analysis, clinical genotyping diagnostics, and layer-by-layer directed self-assembly of molecular and nanoparticle entities into higher order structures. Such devices can produce electric fields on their surfaces to transport or bind charged molecules and nanostructures, including DNA, RNA, peptides, proteins, nanoparticles, cells, etc. and also have the ability to carry out directed self-assembly of nanoparticles into multilayer structures, thus combining “top-down” and “bottom-up” technologies for the assembly and integration of nanocomponents into higher order structures.

Section VII on Genomic Engineering and Systems Biology is composed of five chapters (23 to 27), which present the state-of-the-art of these frontier fields. These chapters cover the steps involved in systems biology research, use of bioinformatics and systems biology to obtain the design principles of living systems, application of synthetic biology to study bioengineering at the genomic level, modeling the influences of genes and genomics in the context of a larger biomolecular system or network, and development

of novel genomic technologies for personalized medicine. This section provides an outstanding collection of cohesive and mutually reinforcing chapters that introduce this important new field of genomic engineering and systems biology that transects life sciences, medicine and engineering.

Chapter 23. *Systems Biology: A Four-Step Process*, by Jennifer L. Reed and Bernhard O. Palsson: Systems biology focuses on the study of biological networks through the processes of (1) network reconstruction, (2) computer model formulation, (3) hypothesis generation, and (4) experimental validation. The first two steps involve identification of components and their interactions, and the result is network reconstruction: an accounting of all components and their interactions comprising the network. From this network reconstruction, an *in silico* model can be generated (step 3) to be used to predict and analyze the behavior of biological systems (step 4). The chapter concludes with a discussion of systems biology applications to address specific biological and industrial questions.

Chapter 24. *Bioinformatics and Systems Biology: Obtaining the Design Principles of Living Systems*, by Shankar Subramaniam: Because of the need for living systems to self-organize and self-evolve, the coupling between multiple time or length scales are non-hierarchical. Events that happen in seconds and minutes give rise to processes that occur in days to weeks. Processes that are traceable to a single cell can result in a systemic response spanning the entire physiology. The blueprint for continuous adaptation, error-checking and optimization of the system is built into living systems such that they sample infinite number of different states. Yet the end-point physiology is often similar or even identical. This implies that multiple solutions lead to nearly the same optimality and behavior of the system. This chapter explores the features of living systems from an engineering and design perspective and attempts to identify methods that can be used to decipher the rules that govern living systems.

Chapter 25. *Synthetic Biology: Bioengineering at the Genomic Level*, by Natalie Ostro, Mike Ferry, Scott Cookson, Tracy Johnson, and Jeff Hasty: The developing discipline of synthetic biology attempts to recreate in artificial systems the emergent properties found in natural biology. Because the genetic networks in cells are complex, redesigning simpler synthetic systems for study is a valuable approach at the genome and gene network levels. Recent activities on designing synthetic gene networks that mimic the functionality of natural systems are not only easier to construct, but also make them more amenable to tractable experimentation and mathematical modeling. The construction and testing of artificial systems resembling natural systems promise to advance our understanding of how biological systems function by providing information about cellular processes that cannot be obtained by studying intact native systems.

Chapter 26. *Network Genomics*, by Trey Ideker: Network genomics models the influence of genes and genomics in the context of a larger biomolecular system or network, which is a comprehensive collection of molecules and molecular interactions that regulate cellular function. This approach allows us to experimentally measure and define biomolecular interactions at large scale. Once all of the interactions present in a

network have been catalogued, it would be possible to ask critical questions on topological structure of the network, signal transmission through the network, and evolutionary conservation of parts of the network. Most importantly, the interaction network can be used as a storehouse of information from which to extract and construct computer-based models of cellular processes in health and disease.

Chapter 27. *Genomes, Genomic Technologies and Medicine*, by Xiaohua Huang: The sequencing of the human genome was one of the greatest breakthroughs in the last century. Genome sequencing with currently available technologies, however, remains slow and expensive for routine sequencing of individual human genomes for biomedical applications. This chapter describes the author's strategies and recent progresses in engineering the next-generation technologies for genome sequencing and for digital enumerations of the molecular components in the cells. Micro- and nano-technologies are used to engineer fully automated, miniaturized "lab-on-a-chip" devices to enable massive parallel manipulations and analyses of biological molecules on an unprecedented scale so that each individual human genome can be sequenced for as little as US\$1000.

Section VIII. Socio-economical Aspects of Bioengineering is composed of three chapters (28 to 30), which present several important non-technical subjects on ethics for bioengineers, bioengineering entrepreneurship, and bioengineering translation. These are very valuable topics for the bioengineers in translating their scientific knowledge to practical applications.

Chapter 28. *Ethics For Bioengineers*, by Michael Kalichman: Adherence to ethical principles is essential in bioengineering research and practice. Although news media reports on ethical violations, misconduct, etc. are typically in high profile areas such as politics, sports, and business, scientists and engineers are not immune from lapses of good judgment. The primary goal of science and engineering is to generate new knowledge for the benefit of humankind. Scientists and engineers should be particularly concerned about the integrity of their disciplines and resist the temptation for misrepresentation. The challenges are to identify the ethical dimensions of the work, to be aware of how to avoid the unethical pitfalls, to develop the skills for ethical decision-making, and to be clear about the obligation to act responsibly. Integrity is central to what it means to be an outstanding bioengineer.

Chapter 29. *Opportunities and Challenges in Bioengineering Entrepreneurship*, by Jen-Shih Lee: The contributions made by biomedical engineering entrepreneurs have improved the understanding of biomedical sciences and also health care for people. This chapter reviews some of the innovations made by the biomedical engineering industry and viewed by physicians as significance in improving the health of their patients. Two innovations, cardiac pacemakers and hemodialysis, are highlighted to elaborate on their entrepreneurial growth into billion-dollar industries. Pointers are offered for readers to evaluate the chance of success for their inventions and to gain insights on the commitment required for entrepreneurship. The chapter concludes with the heading

“Biomedical Engineers Mean Business” to encourage bioengineering students to consider entrepreneurs as their career option when opportunities arise.

Chapter 30. *How to Move Medical Devices from Bench to Bedside*, by Paul Citron: Although there are similarities in how any new technology in any industry migrates from Research and Development (R&D) to the ultimate customer, the medical device industry has certain elements that are unique to it. Understanding these factors and accommodating them as an integral part of the business development plan can make the difference between a mere laboratory curiosity and an innovation that serves the needs of seriously ill patients, while producing financial returns for the industry at the same time. This chapter addresses some of these factors that are unique to the medical device industry and how they relate to the success of the innovation process.

In summary, the 30 Chapters in eight sections of this book provide a rather comprehensive and up-to-date coverage of the current state of bioengineering, showing the rapid advances in the field and the great excitement and tremendous promise it holds for the future. There is no limit in the development of bioengineering, and it is all up to the imagination and innovation of the scientists and students.