Preface

Physiological processes in living systems involve the complex interactions of electrical activity, chemical reactions, and physical phenomena such as mass, momentum, and energy transport. Deviations of any of these processes from their normal states may result in the initiation of diseases. A thorough understanding of physiological processes as they occur in the normal, healthy state as well as under pathological conditions is necessary so that diseases can be detected early enough for interventions to be efficacious. An understanding of complex physiological functions is also vital in the design and development of implants such as vascular stents and heart valve prostheses in human circulation and similar devices in other organ systems. In vivo and in vitro experimental studies, and in recent decades computer simulations, have provided valuable insight into the complex functional physiology and pathophysiology, and our knowledge in these areas continues to grow rapidly. However, in vivo experiments in human subjects and animals require ethical considerations, and the data obtained from in vivo experiments are limited due to practical considerations. In vitro experiments often require expensive equipment such as particle image velocimetry (PIV) systems, and yet there remain limitations in data acquisition due to restrictions of optical access to the areas of interest.

Recent advances in medical imaging instruments, such as magnetic resonance (MR), computed tomography (CT), and ultrasound imaging systems, have improved both the spatial and temporal resolution of the image data that can be acquired. With the appropriate acquisition protocol, these instruments can acquire 3D (volumetric) and even 4D (volume data plus time) data with exquisite anatomic detail. The image data can be visualized using computer graphics techniques to show geometric information and can be processed to provide realistic anatomic models for subsequent computer simulations that explore physiologic function.

With the advent of high-speed computers, computational simulations are increasingly playing a major role in our ability to analyze the physiological processes in the visceral organs and in the human musculoskeletal system. Computational simulations, with appropriate experimental validation, are being increasingly employed for various applications in human health care and have enabled us to reduce the number of animal models required for such studies. It is clear, however, that modeling of biological systems is an extremely challenging enterprise, given the complexity

of such systems and the essential roles played by genetic factors and biological variability. Therefore, while a truly "accurate" model of a physiological system or process is very difficult to achieve, there is immense value in developing computational models that can capture essential features of the behavior of a system under well-defined physicochemical conditions. Computer simulations (1) are relatively inexpensive; (2) can cover wide ranges of parameter spaces; (3) can be improved over time with improved inputs and other information from experiments or with advances in modeling techniques, numerical methods, and computer hardware; and (4) can provide information on flow and stress fields that are difficult to measure or visualize.

The development of computational techniques and advances in hardware in terms of speed and memory have therefore established computer simulations as a strong source of knowledge regarding the behavior of biological systems. In fact, the current phase of computational developments is directed toward enabling increasingly sophisticated representations of biological systems. A particular case is that of multi-scale modeling of such systems. Physiological processes in living systems vary over a wide range of temporal and spatial scales. For example, chemical reactions that take place at a subcellular level require analysis at a timescale on the order of nanoseconds and at spatial dimensions on the order of nanometers. On the other hand, functional physiology of visceral organs such as the human heart involves a timescale on the order of seconds and at dimensions on the order of centimeters. Disease processes such as atherosclerosis, a common arterial disease in humans, develop during a time span of several years. Computational simulations on spatial and temporal scales ranging from nanometers to meters and nanoseconds to years are continuing to be developed, and strategies for integrating both spatial and temporal scales are being explored. In the last five decades, the explosion of new imaging modalities for structural and functional imaging of organs in the human body has also provided additional information for simulations attempting to model complex anatomy and physiology. It can be anticipated that computational simulations will increasingly play a vital role in the area of human health care.

In this book, we address the current status and possible future directions of simulations that have been employed and are continuing to be developed for applications in the human cardiovascular and pulmonary systems. In these two systems, simulations involve the description of the complex fluid flow (blood flow in the cardiovascular system and air flow in the pulmonary system), the mechanics of the soft tissue (vessel and airway walls, cardiac structures, and lung tissue), and the constant interaction between fluids and soft tissue. Typical disease processes, such as atherosclerosis in the human arteries and emphysema in the human lungs, result from alterations at the microstructural level with alterations in viscous properties and mass transport within local regions. Realistic simulation of the physiology and alterations resulting in the initiation and development of disease processes requires the following:

a. Acquisition of images of the organs of interest employing appropriate imaging modality, employment of state-of-the-art image processing and segmentation,

and reconstruction of morphologically realistic three-dimensional (3D) geometry of the region of interest as a function of time.

b. Appropriate boundary conditions (pressures, flow rates, etc.) obtained from physiological measurements.
c. Development of computational techniques for the fluid flow (e.g., to represent blood rheology in the human circulation and turbulent compressible flow analysis for transport of air in the lung airways), the soft tissue (nonlinear anisotropic material description for the cardiac and blood vessel structures and the pulmonary airways from the trachea to the alveolar sacs), and the fluid–structural interaction analyses.
d. Validation of the computational techniques with appropriate experimental or computational simulations, before the application of the simulations, to describe the various physiological and pathophysiological processes.

The chapters to follow in this work are divided into three sections:

Part I deals with image data acquisition and geometric reconstruction commonly employed in the diagnosis and treatment of cardiovascular and pulmonary diseases. Chapter 1 discusses commonly employed imaging modalities used for anatomical and functional imaging of these two-organ systems, as well as trade-offs between spatial and temporal resolution, invasiveness of the imaging technique, and the use of ionizing vs. non-ionizing radiation. Chapter 2 focuses on contemporary image analysis and data processing techniques in order to identify anatomic structures in the images, delineate region boundaries, and construct three-dimensional geometric representations of regions of interest to be employed in the simulations.

Part II consists of discussions of state-of-the-art computational techniques for biological soft tissue, biological fluid, and the analysis of interaction between the fluid and the surrounding tissue. Chapter 3 presents the numerical approaches for solving the Navier–Stokes equations at two distinct scales, viz., the large-scale system that applies at the level of large blood vessels and prosthetic devices, and the small-scale systems that apply to the microvasculature. Chapter 4 details the modeling and solution of the equations governing the dynamics of soft tissue in the cardiovascular system. Chapter 5 focuses on the issue of fluid–structure interactions and distinguishes three types of techniques used to simulate the presence of structures immersed in blood flow. Issues pertaining to the behavior of the fluid–structure coupled solutions as they are influenced by the properties of the immersed solid are discussed.

The majority of the simulations published to date are focused mainly at the organ level where the biological soft tissue as well as the fluid can be treated as a continuum. There are limitations imposed on such simulations due to various practical constraints, including computer memory, processing speed, modeling uncertainties and complexity, biological variability. Even with the increasing speeds and memory densities of state-of-the-art computers, with the finest possible mesh density in the computational simulations, organ systems can at best be resolved down to dimensions in the order of millimeters—i.e., cellular and subcellular phenomena need to

be modeled. However, in the last several decades, our knowledge of the physiological functions and pathological processes at the cellular and subcellular levels has also increased significantly. On the horizon of the computational landscape lies the possibility of linking computational analyses from the organ level (i.e., at the length scale of meters) all the way through to the cellular and subcellular levels (at the length scales of microns) and in time from nanoseconds to disease evolution scales. For example, numerous studies have focused on the relationship between the shear stress induced by the blood flow on the endothelial cells and the shear stresses computed by the simulations at the various arterial segments, as these are related to morphologically observed sites of atherosclerotic plaque development. Numerous experimental studies and simulations have also been employed at the level of endothelial cells in order to understand the response of the cells to external stimuli in the form of structural changes as well as to understand chemical alterations and the release of various growth factors and other enzymes. Recognizing that it is beyond the capabilities of even state-of-the-art high-performance computers to incorporate events at the subcellular level to those at the organ level through direct numerical computations, multi-scale simulation techniques are being investigated. Chapter 6 attempts to sketch the outlines of such a multi-scale modeling effort as it applies to the transport of blood at the micro- and mesoscales. The challenge of connecting these efforts to the large-scale blood flow simulations detailed in Chapters 3 and 5 lies at the frontier of multi-scale modeling.

The focus of Part III is on the application of computational simulations to a range of problems often encountered in the human circulatory and pulmonary systems. Chapter 7 addresses the current status of the simulations on our understanding of the arterial blood flow and the relationship between fluid-induced stresses and atherosclerotic plaque development. Topics include three-dimensional reconstruction of coronary arterial segments and simulation of coronary flow dynamics, flow simulations in the aorta and arterial bifurcations, and image-based simulation of abdominal aortic aneurysms (AAA). Models to analyze the endovascular implants for treating AAA and bypass grafting for the treatment of arterial occlusions are also discussed in this chapter. Detailed treatment of the biomechanics of both AAA and cerebral aneurysms is the topic of Chapter 8. The biomechanical modeling of aneurysm segments includes the effect of the material property of diseased arterial segments and prediction of rupture of aneurysms. The effect of alterations in the fluid flow on the biomechanics of the aneurysms is also discussed in detail in this chapter. Chapter 9 deals with the application of computational simulations for interventional treatments. Topics addressed in this chapter include application of modeling and simulation to assess atheromatous plaque vulnerability to rupture, mechanical effects of balloon angioplasty, and the design of endovascular stents that are implanted after angioplasty to open occluded arterial segments. In the second part of the chapter, the use of simulations for the surgical planning of single ventricle heart defect (SHVD) is described. As discussed with specific examples, rapid development of other patient-specific applications on interventional techniques and surgical planning is anticipated in the near future. The focus of Chapter 10 is on

the application of modeling and simulation toward an understanding of the biomechanics of the respiratory system and the complex relationships between pulmonary anatomy, tissue dynamics, and respiratory function, as well as on how these relationships can change in the presence of pathological processes. Chapters 11 and 12 deal with the biomechanics of the heart valve function. The native heart valves have a complicated three-dimensional geometry. Since diseases of the valves are predominant in the left heart, the functional biomechanics of the aortic and mitral valves are of interest in increasing our understanding of the function of the healthy valve, the mechanical factors that contribute to the valvular diseases—such as calcification of the leaflets—and valvular regurgitation. These dynamic simulations have potential applications in the planning of patient-specific valvular repair strategies as well as in the development of tissue-engineered valve replacements. The dynamic simulations of the heart valves are challenging, requiring the inclusion of the entire valvular apparatus including the annulus, leaflets, and the ascending aorta for the aortic valves, and the leaflets, annulus, chordae and the papillary muscles for the mitral valves, as well as the development of accurate fluid–structure interaction analysis. These topics are covered in Chapter 11 along with the potential applications on the improved designs for biological valve prostheses. Simulations to understand the cause of thrombus deposition, a continuing and significant problem associated with mechanical valve prostheses, and the simulations toward our understanding of the fluid mechanical factors responsible for the same is the topic of Chapter 12.

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