Advances in medical technologies such as noninvasive imaging have had a proven impact on diagnosis, surgical planning, and clinical management with resultant improvements in clinical outcomes. In research, new and improved imaging modalities, combined with novel genetically engineered animal models and recent advances in genomic and proteomic profiling, are increasing our integrative knowledge of pathophysiology from the level of molecular networks to organ systems scales. This has led many workers to suggest that these advancements may accelerate progress to personalized and predictive medicine [2].

In traditional medicine, findings from large clinical trials determine clinical treatments. Based on a trial, a particular therapy may benefit a majority of patients, but differences between individuals can dramatically impact the outcome and efficacy of a specific therapy [5]. The characteristics of an individual undergoing therapy likely differ from the mean of the clinical trial population, thus the therapy may not benefit every patient, or worse, may even complicate the disease process. Physicians therefore take into account differences like gender, weight, height, and age in their clinical decisions, but numerous other patient characteristics – not necessarily of pathological nature – may still lead to adverse effects. Personalized and predictive medicine tries to fill that gap by using information from that patient’s gene or protein profile.

In a parallel development, ongoing improvements in computation power have facilitated the solving of computational models of physiology of increasing complexity (for example, the high-performance Graphical Processor Unit (GPU) Radeon R800 of ATI from 2009 is about 50 billion times faster than the IBM 1620 from 1961). For many models in physiology, it is impossible to find an analytical solution and computers are used to obtain numerical solutions. Many computational models of physiology are written in terms of coupled ordinary and/or partial differential equations (ODEs and/or PDEs). An example of a set of coupled ODEs is the description of sodium and potassium ion kinetics through nerve membrane (with time as the independent variable), proposed by Hodgkin and Huxley [4]. A partial differential equation is an equation where a function depends on more independent variables. An example of a PDE is the monodomain equation that describes the propagation of cellular transmembrane voltage as a function of three spatial dimensions and time. One of the most used computational tools for solving
PDEs on a complex domain, such as the heart, is the finite element method. In the finite element method, the entire geometric reconstruction of the anatomy (obtained, for example, by MRI) is subdivided into smaller elements, with bordering point-wise nodes to construct a mesh [3]. The solution is approximated on the mesh by linear or higher-order functions, which are defined in the elements. The finite element method is used for models throughout this book to solve, for example, for atrial electrophysiology (Chap. 4), ventricular mechanics (Chap. 8), ventricular electrophysiology (Chap. 9), ventricular electromechanics (Chaps. 9–12), and blood–wall interactions in abdominal aortic aneurysms (Chap. 6).

Computational models of physiology are based on physico-chemical principles and are testable, reproducible, and allow easy manipulation of parameters without affecting others [1, 6]. Such models have already proven to be useful in elucidating biological mechanisms in health and disease [11] from gene to whole-organ level [10]. For example, a sensitivity analysis with a computational model of dyssynchronous heart failure showed that ventricular dilation and electrical dyssynchrony combined, synergistically decreased regional cardiac function [7]. Clinical indices of regional cardiac function that are based on strain magnitudes are sensitive to this combination, whereas indices that are based on strain timing are insensitive to this combination. The study also showed that strain magnitude-based indices reflect better the relative nonuniform distribution of regional work in the myocardium. These findings might explain why strain magnitude-based indices of cardiac regional function are better predictors of reverse remodeling in cardiac resynchronization therapy [8].

Because of these advancements in technology and increased knowledge of physiological mechanisms, it has been proposed that computational models of physiology tailored to individual patient characteristics will eventually prove to be a valuable and versatile technology that improves medical care in a myriad of disciplines [9] and especially in cardiology could serve as an enabler of personalized medicine [11]. This book therefore focuses on the potential of patient-specific computational models of cardiovascular physiology to predict or optimize outcomes of clinical treatments. Two main reasons underlie this choice: first, cardiovascular disease is still the leading cause of death in most industrialized countries; second, cardiac models represent one of the most advanced areas of computational biology, bridging from the subcellular to the circulatory level [12], making them an excellent candidate for mechanistic patient-specific modeling. Chapter 1 provides an overview of imaging modalities, which can be used to create patient-specific models. It also discusses anatomical models already being used in the clinic, which are used to visualize impulse conduction in the atria measured by electroanatomic mapping. Finally, electrophysiology research is discussed that may be translated to the bedside.

It is important that for the creation of a patient-specific model, patient burden – i.e., due to measurements of a patient’s state – is kept to a minimum. Chapter 2 focuses on obtaining patient-specific cardiovascular models in which adaptation rules are used. This approach leads to a reduction in the number of measurements that are needed to adjust for patient-specific fitting and conventional
measurements can be used much more efficiently, enabling to obtain hidden
diagnostic information that normally would depend completely on invasive tech-
niques. In addition, the model proposed in this chapter may also be used to assess
different treatment protocols by simulation of the prognosis after intended
treatments.

Chapter 3 provides an overview of techniques related to modeling of normal and
diseased cardiac cells focusing on approaches that have a high potential for clinical
translation. The chapter discusses how cellular structure and function are altered in
cardiac disease, methods for measuring these alterations, and briefly discusses math-
ematical approaches for functional modeling of (altered) cellular electrophysiology.

An example of a future application of a mechanistic model of atrial fibrillation –
and how it may be used in the clinic – is given in Chap. 4. Different types of
sustained atrial fibrillation dynamics were simulated and the results agreed with
those observed in the clinic.

Whereas the majority of recent patient-specific models include 3D representa-
tions of organs [9], Chap. 5 discusses the application of simpler models in critical
care. This chapter illustrates several hemodynamic and glucose/insulin models that
have been developed and already applied in critical care settings to manage patient
homeostasis. Although many of these simpler models have existed for decades,
their use in critical care patient-specific modeling has become available only
recently.

The risk of abdominal aortic aneurysm (AAA) rupture is nowadays mainly esti-
mated based on the maximum diameter of the dilated aorta. Chapter 6 describes the
current status of AAA wall stress analyses – obtained from patient-specific models
– including the discussion of relevant factors like initial wall stress, nonlinear mate-
rial behavior, and thrombus. The chapter also discusses the clinical perspectives of
AAA wall stress analysis with respect to AAA rupture risk and growth.

Not all model parameters can be obtained patient-specifically. Therefore, a need
exists for a publicly accessible database that offers supplemental data. Chapter 7
describes the Cardiac Atlas Project (CAP), which is a web-accessible structural and
functional atlas of the normal and pathological heart for clinical, research, and
educational purposes. This atlas’ purpose extends beyond the “normal” database:
an initial goal of the atlas is to facilitate statistical analysis across population groups
of regional heart shape and wall motion characteristics, via the application of math-
ematical modeling tools.

A noninvasive method for estimating myocardial material properties in vivo
would be of great value in the design and evaluation of new surgical and medical
strategies to treat and/or prevent heart failure. In Chap. 8, finite element models of
a normal human subject and a patient with diastolic heart failure were created using
tagged magnetic resonance (MR) images and noninvasive left ventricular (LV)
pressure measurements. Diastolic and systolic myocardial material parameters
were estimated by matching LV volumes and stresses were evaluated.

One of the parameters that cannot be obtained directly and patient-specifically
is myocardial fiber architecture in the ventricles. Chapter 9 describes a method for
constructing models of whole-heart electrophysiology and electromechanics from
structural and diffusion tensor magnetic resonance images acquired ex vivo, and presents a processing pipeline for estimating patient-specific myocardial fiber orientations from images scanned in vivo. These modeling techniques in combination with the proposed methodology for estimating patient-specific myocardial fiber orientations constitute a step toward patient-specific simulations of cardiac electrophysiology and mechanics.

Of all heart failure patients, those with the additional complication of dyssynchronous contraction (often due to a conduction defect such as bundle branch block) have the worst prognosis. Cardiac resynchronization therapy (CRT) involves placing a pacemaker to improve the synchronicity of cardiac contraction. It has recently been shown that CRT is an effective method of treating patients with dyssynchronous heart failure, inducing significant reductions in morbidity and mortality in large clinical trials. However, clinical trials have also demonstrated that up to 30% of patients may be classified as non-responders. The development of patient-specific models may maximize response to CRT. In Chap. 10, a computational model of cardiac electromechanics based on a clinical case was successfully used to predict the acute effects of ventricular pacing on cardiac function with four different pacing conditions.

The three leading causes of death in most industrialized countries (cardiovascular disease, cancer, and stroke) involve an hypoxic response. Individual patients can vary tremendously in their response to hypoxic exposure, and to therapies targeting hypoxic pathways. In Chap. 11, the sources of patient variability related to oxygen sensing and response are discussed and computational modeling approaches are addressed. These models capture essential processes involved in hypoxia and microvascular dynamics, and offer promise as tools to advance patient-specific therapeutic design.

Building a patient-specific model of the heart involves many steps from data acquisition to model result. Chapter 12 discusses a multiscale framework for modeling of cardiac electromechanics that includes a model database, image segmentation, and several mechanistic models from cell to system.

References


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