

Preface

This book contains a selection of the contributions presented at MPF2013 in June 2013 in Chia Laguna (Sardinia), the fifth edition of a series devoted to the mathematical and numerical modeling of physiological flows.

The focus of this fifth symposium was on data analysis, digital imaging, mathematical models, and numerical simulation of the human circulatory system as a whole, and more specifically on cardiac mechanics and electrophysiology, heart perfusion, ventricular fluid dynamics, fluid-vessel wall interactions, multiscale analysis of blood rheology in small vessels, and system integration. The contributions presented in this book provide a very interesting overview on the state of the art of some of these topics and contain several original contributions to the field. What follows is a short account of the most relevant contents of each chapter.

In the first chapter, written by N. Trayanova and coauthors, it is explained how biophysically detailed simulations can clarify experimental observations and help reveal how organ-scale arrhythmogenic phenomena emerge from pathological effects at the tissue, cell, and protein levels. This “virtual heart” approach seeks to use experiments and simulation to quantitatively characterize the action potential response of cardiac cells to electrical stimuli.

The construction of multiscale models of the electrical functioning of the heart aims at representing the integrative behavior from the molecule to the entire organ and is an essential methodological step towards clinical applications of cardiac organ modeling. This chapter focuses on both achievements in mechanistic understanding of heart function and dysfunction and on the trends in the computational medicine aspect of biophysically detailed cardiac modeling applications.

Key in attaining predictive capabilities of multiscale biophysically detailed cardiac models at the level of the organ has been the use of geometrically realistic (typically MRI- or CT-based) models of the ventricles and the application of diffusion tensor imaging to measure the anatomy, fiber, and sheet structure of the heart in *ex vivo* studies. Models of cardiac function have benefitted significantly from this revolution in medical imaging. Cardiac models have been used to gain insights into mechanisms of arrhythmia in many disease settings and to understand how external currents can terminate ventricular arrhythmias.

The most frequently applied approach to model the mechanics of cardiac tissue is based on continuum mechanics. There is, however, another possibility based on the use of discrete mechanical approaches. In Chapter 2, written by A.V. Panfilov and coauthors, discrete mechanical models are proposed for the simulation of the mechano-electrical feedback (MEF) on the process of spiral wave formation in cardiac tissue. The two principal ways of formulating discrete mechanical models of cardiac tissue are presented. The so-called off-lattice models, which describe cells as not being restricted to a regular grid, allow the description of biological phenomena such as cell division and growth without causing immediate mechanical long-range effects. Lattice-based models are instead more appropriate for describing mechanical long-range interactions such as the finite elastic deformations of the heart tissue.

MEF is the effect of the deformation of cardiac tissue on its excitation processes. This chapter shows that MEF substantially affects the process of spiral wave initiation and discusses several new mechanisms that are found using the proposed discrete mechanical approach.

Another study concerns the effect of structural changes in cardiac tissue on the heart's mechanical properties and, further, how these effects may cause cardiac arrhythmia. The authors also propose and investigate how to couple a discrete mechanical model to a reaction-diffusion model for continuous electrical pulse propagation.

In Chapter 3, N. Smith and co-authors investigate the mechanisms governing coronary blood flow in healthy and diseased coronaries, with the aim of understanding the relationship between the structure of the coronary vasculature and its function, which exhibits distinct characteristics over multiple scales. More specifically, the coupled fluid-structure model of coronary flow outlined in this chapter aims to bring together the principal components of the system to establish an integrated framework for investigating and, later, predicting myocardial perfusion on an individual-specific basis in a physiologically relevant manner. To this end a model of flow in macroscopic arteries [the left anterior descending (LAD), left circumflex (LCx), and right coronary (RCA) arteries], a multicompartiment Darcy model representing myocardial perfusion over a range of vessel sizes, and a poroelastic model capturing the flow phenomena in the beating heart are proposed. Wave intensity analysis and tissue signal in perfusion MRI, both of which representing the current state of the art in invasive and noninvasive cardiological exams, create a basis for clinical translation of the present work.

In Chapter 4, written by F. Nicoud and coauthors, the geometry of the heart cavities and associated wall motion are extracted from 4D medical images while the valves of the heart are simulated by using low-order geometrical models. Equations are solved using a fourth-order low-dissipative finite-volume scheme and a mixed arbitrary Lagrangian-Eulerian/immersed boundary framework.

Recent technological innovations in imaging techniques have provided valuable opportunities for direct noninvasive *in vivo* assessment of hemodynamics. Blood flow velocities can be measured *in vivo* using phase-contrast magnetic resonance. Medical images are then used to generate a moving patient-specific domain, in which the blood flow equations are solved. Heart geometry movements are generated from a 4D sequence. The authors devote specific attention to the generation of high-quality

mesh that deforms consistently with the heart motion. On such a high-quality grid the unsteady turbulent flow is simulated by a large eddy simulation technique in the left heart described by ECG-gated 3D CT scan. The results show that fluid inertia makes the flow differ from one cycle to another in the upper part of the left atrium, where the collision of the jets issuing from the pulmonary veins makes the flow chaotic. In the left ventricle, velocity fluctuations are reported mainly during late diastole.

In Chapter 5, G. Karniadakis and H. Lei present a comprehensive computational framework based on the mesoscale dissipative particle dynamics (DPD) method to investigate the three key hallmarks (heterogeneous morphology, rheology, and vaso-occlusion) of the hematological disorder sickle cell anemia (SCA). The multiscale nature of the DPD model allows the authors to address the different dynamic processes over a wide range of length and time scales involved in this disease. A coarse-grained stochastic model is built up to represent the development of the intracellular aligned sickle hemoglobin polymer domain for sickle red blood cells (SS-RBC). Using only the experimentally measured bulk growth rate of the sickle hemoglobin polymer as the input, the model successfully predicted the typical sickle cell morphologies without introducing further ad hoc assumptions. The inferred cell morphologies enabled the authors to further explore the rheology of heterogeneous SS-RBCs suspensions with accurate prediction of the shear viscosity for the different cell rigidity and morphologies. In particular, their simulations of the hemodynamics of SS-RBC suspensions suggested that the sickle/elongated SS-RBC suspension, once in microcirculation, does not induce vaso-occlusion by itself. Moreover the flow resistance induced by this cell group could be even lower than that induced by other cell groups. Despite being counterintuitive, this result is consistent with recent experimental studies on vaso-occlusion crisis.

In Chapter 6, written by A. Gizzi and coauthors, the mathematical model formulation of the mechanochemical coupling in single cardiomyocytes based on an active strain approach has been analyzed and extended to realistic three-dimensional geometries. The proposed activation mechanism is consistent with a thermodynamic framework entailing a nonlinear coupling among calcium dynamics and local stretches. The continuum approach adopted is along the line of recent bio-chemomechanical models of single cells formulated in terms of active-strain hyperelasticity. The model is capable of reproducing the propagation of calcium waves and the corresponding spontaneous contraction within the cell, as well as the bending behavior, peculiar features of a three-dimensional structure. A finite element method is used to discretize the model equations; a set of numerical experiments comparing two- and three-dimensional reconstructed cardiomyocyte geometries provide evidence of the main features of the model and its ability to predict calcium propagation patterns and contractility, in good agreement with experimental observations. Different boundary conditions are considered to reproduce physiological constraints. The corresponding resulting stress patterns are the analyzed.

Chapter 7, written by K.A. Mardal and O. Evju, develops a critical review on the assumption of laminar flow in physiological flow applications. Most fluid flows in our human body are believed to be laminar in healthy individuals, an exception being the blood flow in the heart and aorta. On the other hand, various pathologies, such

as atherosclerosis and aneurysms, involve anatomical alterations causing distributed flow and possibly even turbulent flow. This may lead to an unhealthy mechanotransduction (the process whereby cells convert mechanical stimuli to chemical activity, which is vital in the remodeling that occurs in vessels), causing remodeling of the vasculature that again increases flow disturbances. Recent research has therefore challenged the assumption of laminar flow in such pathologies and placed the focus on the possible role of transitional or turbulent flow.

While the laminar regime and in many applications the fully developed turbulent regime are reasonably well understood from both a modeling and a numerical point of view, the transitional regime with occasional turbulence poses additional challenges. Modeling is difficult in particular because it is challenging to precisely predict the onset of the turbulent spots. Instead of modeling the turbulence, one might increase the resolution in space and time and resolve all scales of the turbulent flow numerically, a technique called direct numerical simulation (DNS).

The authors address blood flow in cerebral aneurysms, discussing the consequences of the assumption of laminar flow, and validate the use of stabilization techniques and time discretizations on numerical dissipation. They also review clinical and biomechanical findings suggesting that transitional flow is common or at least not unusual in several pathologies. Finally they discuss cerebral aneurysms in depth and show that for some aneurysms transition may occur at a Reynolds number as low as 300.

In Chapter 8, P. Zunino and coauthors investigate the effects of poroelasticity on fluid-structure interaction in arteries. Blood flow is modeled as an incompressible Newtonian fluid confined by a poroelastic wall. A two-layer model is used for the artery, where the inner layers (the endothelium and the intima) behave as a thin membrane modeled as a linearly elastic Koiter shell, while the outer part of the artery (the media and adventitia) is described by the Biot model. The assumptions are made that the membrane can transduce displacements and stresses to the artery and that it is permeable to flow. Because of poroelasticity, the interaction of the fluid and the structure at the interface is more complicated than in the case of a standard fluid-structure interaction problem. The weak enforcement of interface conditions based on Nitsche's type mortar techniques guarantees stability. In particular, the authors are interested in qualitatively characterizing how the presence of intramural flow coupled to the arterial wall deformation affects the displacement field as well as the propagation of pressure waves. Their results suggest that accounting for the intramural plasma filtration significantly affects the arterial wall displacement as well as the propagation of pressure waves. However, it is observed that resorting to a poroelastic material model is not essential to capture these effects. A simpler model based on Darcy equations combined with approximate kinematic conditions may be adequate to capture similar effects.

Chapter 9, written by Y. Vassilevski and coauthors, addresses the process of generating anatomical meshes of the entire human body. According to the authors, the ideal approach for construction of an anatomically correct 3D geometric model is to produce 3D geometry from individual medical images (CT, MRI, or other slice-like data). This requires strong involvement of human expertise. Moreover, such data

can be unavailable or may feature low quality due to several factors. The authors propose an alternative approach that consists in fitting a reference anatomically correct model based on either individual data or detailed post-mortem examination or a conventional database.

For patient-specific body meshing the authors adopt a four-stage algorithm which relies on the assumption that the patient has the same structural body composition as the reference VHP (the Visible Human Project) model, i.e., the same set of tissues and organs. First, they apply the semiautomatic segmentation of the reference VHP images. Second, they perform the anthropometric mapping of the reference model to the patient dimensions. Third, for selected cross-section planes they generate a piecewise affine transformation to map the reference segmentation to the patient segmentation on the basis of user-defined control points on both references and patient images.

For patient-specific vascular network reconstruction the open source library VMTK is adopted to produce vascular centerlines on the basis of CT/MRI data followed by the automated “skeletonization” algorithm. The produced vascular graph possesses all the necessary geometric data for hemodynamic simulation. The authors demonstrate the applicability of their approach to predictive personalized postsurgical blood flow simulations.

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