Preface

"πᾰντες ανθρωποι του ειδεναι ορεγονται φυσει."
[All men by nature desire to know.]
(Aristotle [−384 – −322], Metaphysics, Book I)

Modeling relies on access to data accumulated on any target object (configuration, structure, controlled functioning, fate under various types of stimuli, reaction to stresses that can be experienced, etc.). Knowledge is associated with a set of conditions: truth, belief justification, reliability, and stability. Understanding does not necessarily bring certitude before validation, especially in the absence of observation data.

Volumes 1 to 4 of this series present events and their molecular participants that govern cell fate — intra-, auto-, juxta-, and paracrine — as well as possible endocrine regulations upon diverse types of stimuli, in the context of modeling and simulations. These events rely on cascades of chemical reactions that successively activate signaling mediators within the cell, at the nanoscopic scale. At the micro- and mesoscopic scale, biological phenomena comprise isolated and collective behavior of cells in interaction with their environment, either apposed cells, or the extracellular matrix. The present volume, Volume 5, treats mural tissues of airways and blood and lymph vessels — events occurring at the mesoscopic scale that can be targeted by mathematical models. Subsequent volumes focus on diseases associated with air and blood flows (Vol. 6) and mechanics of these flows (Vol. 7). Volume 8 is a set of glossaries.

Biological tissues are made up of composite material with different cell types in an extracellular matrix. Both types of tissue constituents — cells and matrix — are reinforced by filaments and fibers. In addition, the extracellular matrix can contain lamellae. Structural hierarchy relies on the multilevel structure of biological tissues. The smallest structural levels are related to biological components, i.e., macromolecules (scale $\mathcal{O}[1]$ nm), microfibrils ($\mathcal{O}[1]$ and $\mathcal{O}[10]$ nm]), fibers ($\mathcal{O}[100]$ nm), lamellae ($\mathcal{O}[1–10]$ µm). The fifth structural level usually corresponds to tissue elementary structure (scale $\mathcal{O}[100]$ µm). Biological tissues are characterized by an optimal combination of configuration and structure at a given time with appropriate chemical and physical features to achieve their functions.

Biological tissues are capable of short- and long-term adaptation (remodeling) to applied constraints that causes change in configuration and structure. These constraints include mechanical stresses. The mechanical behavior of biological tissues depends on (1) type of applied forces (tension, compression, shear, and torsion) and their possible combination; (2) loading orientation, magnitude, duration, and rate; (3) eventual periodicity (frequency); and (4) state of the surrounding environment and organism that regulate perfusion (hence, temperature, moisture, etc.).

The rheological properties of a sample of biological tissues that are related to tissue composition are usually described by a set of parameters (bulk, elasticity, and shear moduli in principal tissue directions;[1] Poisson's ratio, Lamé's parameters, bending stiffness, flexural modulus, ultimate tension, compression, and shear stress; etc.).

Even in normal conditions, biological tissues remodel to adapt to their environment. For instance, the thickness of arterial walls in a given vessel section can vary in the azimuthal direction, as it depends on the local stress field applied by the flowing blood. Tissue engineering that does not incorporate mechanical stresses fails.

Abnormal situations are also characterized by maladaptive tissue remodeling (Vol. 6). Surgical procedures such as grafting and minimally invasive, catheter-based implantation of medical devices such as stents aimed at correcting risky tissue growth can themselves trigger another type of aberrant tissue growth, such as intimal hyperplasia.

Especially when they aim at predicting organ functioning, disease evolution, and drug delivery up to cells with abnormal functioning, mathematical models not only focus on cellular events, but also on biological tissues. Major scientific developments in health technology are aimed at integrating available fragmented data and models to improve medical decision-making and actions (gestures), reduce healthcare costs, and optimize the design of implantable devices.

This strategy copes with many challenges. Among them, modeling that span multiple structural levels (from molecular to entire organ). Therefore, the three basic

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[1] Viscoelastic materials exhibit a phase lag (ϕ) between stress ($\mathbf{c}$) and strain ($\mathbf{e}$):

$$\begin{aligned} \mathbf{c} &= \mathbf{c_{max}} sin\{\omega t\}, \\ \mathbf{e} &= \mathbf{e_{max}} sin\{\omega t + \phi\}. \end{aligned} \tag{0.1}$$

Complex elastic (E^*) and shear (G^*) moduli

$$E^* = E_{Re} + \imath E_{Im}, \quad G^* = G_{Re} + \imath G_{Im}, \tag{0.2}$$

are expressed from tensile ($\{E_{Re}, E_{Im}\}$) and shear ($\{G_{Re}, G_{Im}\}$) storage ($\mathbf{c}/\mathbf{e} \cdot \cos\phi$) and loss ($\mathbf{c}/\mathbf{e} \cdot \sin\phi$) moduli. Storage and loss moduli represent stored and dissipated energy of viscoelastic tissues, respectively. Moreover, viscoelastic materials can be described by a low and a high modulus at high and low temperatures, respectively, and the storage modulus by a low and a high rate modulus.

natural sciences — biology, chemistry, and physics — interact with mathematics to optimize proper descriptions of the functioning and regulation of air and blood flows.

Multiscale computational models currently being tackled include: (1) the heart pump functioning in the normal and diseased states; (2) the transport of drug nanoparticles that target a specific body region; (3) the insertion of an implantable medical device inside a blood vessel, and (4) the transfer of drugs across the arterial wall and of therapeutic aerosols within the lumen and walls of the respiratory tract. However, despite advances in modeling patient anatomy, biophysical models remain difficult to efficiently personalize.

Whereas mathematical models focus on tissue behavior from the nanoscopic to the mesoscopic scale, biomechanical modeling and simulations concentrate on macroscopic events. Pumps and conduits walls are constituted by various types of biological tissues. These living composite materials sense, transmit, and react to forces exerted by flowing physiological fluids, such as air and blood. The behavior of cells and tissues is tightly coupled to flow pattern.

Major features of flows are described by the equations of mass and momentum conservation, the so-called Navier-Stokes equations. However, because of the complicated architecture of networks of large and mid-size airways and blood vessels that are assumed to convey a homogenous fluid, the Navier-Stokes equations cannot be solved analytically and require numerical simulations.

In addition, both air and blood flow inside deformable conduits. Therefore, the fluid dynamics depend not only on the geometry of the computational domain, on the boundary conditions applied at domain inlets and outlets,[2] and on the values of flow governing parameters, but also on the constitutive law of vessel walls, as well as that of blood, when a non-Newtonian behavior must be incorporated, i.e., in the presence of stagnant flow regions.

Blood is propelled from cardiac ventricles into arterial trees during systole once the pressure difference between the ventricular and arterial sides of the ventriculo-arterial valves causes leaflet displacement and change in shape. Flow deceleration then provokes valve closing. The structure of the valved orifice can be divided into four main domains with their own geometrical and rheological properties: arterial root, valve base, leaflet, and coaptation zone (contact surfaces). Therefore, coupling cardiac contraction to blood ejection requires tackling a strong contact phenomenon.

Heart electromechanical coupling provides a good example of a feedback loop. The electrochemical wave caused by activation and deactivation of a set of ion channels, pumps, and exchangers on the surface of as well as inside nodal cells and cardiomyocytes triggers the ventricular contraction that, in turn, strains nodal cells and cardiomyocytes, thereby influencing the activity of mechanosensitive ion channels (mechanotransduction).

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[2]Entry and exit segments should be extended in the vessel axis direction to limit the sensitivity to the boundary conditions in the region of interest and take into account up- and downstream effects of three-dimensional flows.

The respiratory epithelium that covers the luminal face of airways secretes a bilayered fluid-gel coating and surfactant in large and small ducts, respectively. Mucus in large airways clears entrapped particles from the respiratory tract. Surfactant permits a proper inflation and deflation of bronchioles and alveoli.

This set of textbooks devoted to Circulatory and Ventilatory Systems in the framework of Biomathematical and Biomechanical Modeling aims at providing basic knowledge and state of the art on the biology and the mechanics of blood and air flows. The cardiovascular and respiratory systems are tightly coupled, as their primary function is the supply of oxygen (O_2) to and removal of carbon dioxide (CO_2) from the body's cells.

The present volume comprises 14 chapters. These chapters focus on the biological tissues of the cardiovascular and ventilatory apparati (i.e., histology) and their functioning. Chapter 1 covers blood, a concentrated suspension of circulating cells in a solvent, the plasma. Blood is a peculiar type of connective tissue used for transport and body regulation. All blood cell lineages derive from hematopoietic stem cells (Chap. 2). Hematopoiesis thus aims at maintaining a steady cell density in the blood circulation (source term). The structure and function of blood cells — erythrocytes, leukocytes, and thrombocytes — are described in chapter 3. The circulatory network is connected to a specialized plasma-recycling compartment, the lymph collector. The latter conveys the lymph in lymphatic vessels (Chap. 4).

Chapters 5 to 9 cover the structure and composition of the heart and vessel walls. Chapter 5 focuses on cardiomyocyte structure and function. Chapter 6 on heart wall highlights nodal cells that constitute the cardiac natural pacemaker and conduction routes for the propagation of the electrochemical command. Blood vessel walls are studied in chapter 7 with a special emphasis on the blood–brain barrier. Chapter 8 examines the activity of the vascular and respiratory smooth myocytes that regulate the caliber of blood vessels and airways. Endothelial cell at the interface between the flowing blood and vessel wall is assigned to chapter 9. These cells play a role in clotting, extravasation of flowing cells, and transduction of mechanical stresses into chemical cues. Mechanotransduction leads to the synthesis of several substances that regulate the vasomotor tone.

Chapter 10 presents the regulated development of blood (vasculo- and angiogensis) and lymph vessels (lymphangiogensis). Chapter 11 discusses some biological processes, such as tissue growth as well as remodeling and repair, which are common to any body's tissue. The final two chapters are devoted to the coating of the respiratory tract. Chapter 12 focuses on the mucus layer that lies over a periciliary fluid in large airways as well as in medium-sized and small bronchi, while chapter 13 deals with the airway-lining surfactant in pulmonary acini.

Abbreviations and Notation

Common abbreviations such as "a.k.a." ("also known as") are used throughout the text to lighten sentences. Latin-derived shortened expressions are also widely utilized: "e.g." (exempli gratia) and "i.e." (id est) mean "for example" and "in other words", respectively. The notation mode of molecule aliases is introduced in the appendix.

A physical quantity associated with a given point in space at a given time can be: (1) a scalar uniquely defined by its magnitude; (2) a vector characterized by a magnitude, a support, and a direction represented by an oriented line segment defined by a unit vector; or (3) a tensor specified by a magnitude and a few directions. To ensure a straightforward meaning of symbols used for scalar, vectorial, and tensorial quantities, bold face upper and lower case letters **T** and **v** are used to denote a tensor and a vector, respectively, whereas both roman (plain, upright)-style upper and lower case letters designate a scalar.

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[3]CRM (www.crm.umontreal.ca).

[4]TIMS (www.tims.ntu.edu.tw).

[5]Institut National de la Recherche en Informatique et Automatique (INRIA; www.inria.fr).

[6]Centre National de la Recherche Scientifique (CNRS; www.cnrs.fr).

[7]www-roc.inria.fr/reo

[8]LJLL (www.ann.jussieu.fr).

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