Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems 8

Marc Thiriet

Vasculopathies

Behavioral, Chemical, Environmental, and Genetic Factors

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Preface

> Sed ultimus gradus in quem potest artis complementum, cum omni naturae potestate, est prolongatio vitae humanae in magnum tempus. Quod autem hoc sit possibile, multa experimenta docuerunt.
>
> [But the highest degree of the art that the power of nature can reach is the extension of human life for a long period. That this might be possible can be taught by many experiments.]
>
> (J.D. van Hoven [1705–1793] [1])

Precision cardiovascular medicine incorporates differences between individuals to optimize screening, diagnosis, monitoring, prognosis, and therapeutic decisions. Individualized medicine is based on patient features, integrating risk factors, lifestyle, genetic variants, familial context, medical history, and circulating molecular markers (e.g., secreted proteins, microRNAs, long nonprotein-coding RNAs, and released microvesicles) in addition to structural and functional data obtained from clinical examinations, accurate and precise biological measurements (e.g., information related to genomics, epigenomics, proteomics, transcriptomics, and metabolomics), functional exploration, and imaging, along with modeling and simulations.

Important Mendelian diseases are related to single nucleotide variations. Insertions and deletions are also responsible for inherited diseases. Analysis of genotype and phenotype enables mapping of gene variants to disease. Genome sequencing optimized by proper technologies and analysis algorithms, which maximize the sensitivity and specificity, is aimed at enhancing diagnostic sensitivity and medical decision-making, allowing early intervention and precise individualized therapy according to the unique patient genome.

The genome comprises more than 51,000 genes and pseudogenes, about 20,000 of which are protein-coding genes, the size ranging from less than 10 (8 for a transfer RNA) to an order of magnitude of 10^6 base pairs and containing from 1 exon to an order of magnitude of 10^2 exons.

> Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease. (W. Osler (1849–1919) [2])

For example, a loss-of-function polymorphism in the CYP2C19 gene, which is observed in 35% of people of European and African ancestry and 60% of individuals of Asian ancestry, the product of which, a drug processor, reduces the conversion of clopidogrel, an antiplatelet agent used to prevent thrombosis after stent placement, to its active metabolite [3].

Medical strategies are aimed not only at promoting early diagnosis and improving prognosis, but also at avoiding unwanted drug effects. Pharmacogenomics assesses the response of individuals to drugs and identifies patients at risk for adverse reactions to given medications using genetic markers.

In addition, regenerative medicine can use cells of the patient derived from induced pluripotent stem cells, which are transplanted to replace a damaged organ.

Medical and surgical gestures (e.g., catheter-based procedures and minimally invasive treatment of a beating heart) require precision. Surgical planning and design gain from modeling implicated in virtual reality tools and mechanical exploration. These preliminary stages enable us to select the most appropriate surgical path and the most suitable repair technique. Navigation systems guide the surgeon's gestures using imaging. Operating robots receive images of a target organ, analyze its motions, and assist surgical gesture according to these movements. Telesurgery consists of controlling a remote slave manipulator robot, which operates surgical instruments using a master control console. This console measures displacements of fictitious instruments driven by the surgeon and transmits them to the robot.

Personalized medicine relies on a multidisciplinary research. However, the definition of a given noun may vary between disciplines. For example, the use of the terms "oxidative and reductive stress" are not handled in a similar fashion by biologists and chemists. In biology, oxidative stress implies that the production of reactive oxygen and nitrogen species exceeds that of anti-oxidants, an imprecise concept that mentions neither the types of oxidants and reductants involved nor the reactivity [4]. However, reactive oxygen species (ROS) sources, sinks, and fluxes are most often only partly known, and chemical reactions are frequently quite fast. Reductive stress is related to an excess of reducing equivalents that cannot be adequately accommodated by oxidoreductases. On the other hand, the objective of chemists is to describe redox reactions precisely. From a chemical point of view, ROS can oxidize molecules with a more negative redox potential, thereby exerting an oxidative stress, and reduce other molecules with a more positive redox potential, hence imposing a reductive stress.[1] Therefore, the term "redox stress" is preferred.

In a multidisciplinary context, a given name can even describe opposing features. For example, in neuroscience, plasticity is referred to as the adaptation of neuronal circuits to the history of stimuli experienced. At the nanoscopic level, created communication domains disappear when environmental conditions change and reappear once excitations similar to previous stimuli reappear. On the other hand,

[1] Superoxide anion can reduce disulfides and oxidize tocopherol. Hydrogen peroxide can reduce ferryl hemoglobin and oxidize methionine [4].

in rheology, plasticity defines the propensity of a material to undergo permanent deformation under any load, the magnitude of which is greater than the plasticity threshold (also named yield strength and yield point). At the nanoscopic level, the molecular assembly displays irreversible structural changes and cannot return to the initial structure and morphology. In the former case, plasticity is linked to adaptive reversible remodeling, whereas in the latter case, plasticity designates an irreversible state that can lead to material rupture, although at very small strain and stress, the body undergoes an elastic (reversible) deformation (elastoplasticity).

Organ and Physiological Apparatus

The body is made up of many several physiological apparatuses, which have a particular relation to their environment inside the organism, are connected to varying degrees, play a distinct role, and have great importance for the body's survival.

Certain organs are more vulnerable to a given type of disorders than others. This susceptibility is traditionally attributed to intrinsic causes, such as the density of stem cells and cellular turnover rate, and extrinsic factors, such as pollution and lifestyle (e.g., eating habits, cigarette smoking, and alcohol consumption), which do not affect all organs to the same extent.

Large and paired organs with their specific and connected ecosystem may tolerate disorders more easily than small organs, which are critical to organismal survival, especially throughout the reproductive period, the functioning of organs being governed by compromises. For example, anti-cancer protection varies among organs [5]. Cancer is common in the colon, but rare in the small bowel.

Among physiological apparatuses of the human body, the integument limits and protects the organism and serves as a sensory interface with the body's environment. The skeletal (bones and cartilages) and muscular systems (skeletal muscles, tendons, and ligaments) are implicated in the body's structure and motions, the larger bones containing the bone marrow, the production site of blood cells. The nervous and endocrine systems are involved in remote control. The circulatory circuit and respiratory and digestive tracts are responsible for nutrient processing and delivery. The urinary system (kidneys, ureters, the bladder, and urethra) contributes to waste removal, regulates the electrolyte balance and blood volume, and maintains the pH homeostasis and blood pressure. Immunity distinguishes the bodily cells from foreign elements, which are neutralized or destroyed. The reproductive system produces haploid gametes that fuse to form diploid zygotes, engendering a unique new combination of alleles, thus increasing genetic variation among offspring on which natural selection can operate. Human sexual reproduction employs internal fertilization using sexual structures of the male and female reproductive tracts.

Bodily organs, which are mineralized (e.g., skeleton), solid and soft (e.g., brain, kidney, and liver), or hollow (e.g., heart and blood and lymph vessels in addition to the respiratory, digestive, and urinary tract), have a complicated morphology and structure made up of composite materials.

Any physiological apparatus is characterized by a set of major properties.

1. *Diversity*, i.e., a huge between-subject variability in architecture (anatomy), which explains the need for image-based 3D reconstruction for precision medicine (i.e., subject-specific investigation).
2. *Variability*, i.e., permanent adaptation to environmental conditions, means that images acquired at a given time represented not only a model of the reality, but also a frozen structure that neglects the influences acting on a living organ.
3. *Complicated structure and function* are controlled both remotely by the fast-operating nervous and endocrine systems acting in the longer term and locally by a locoregional control exerted by hemodynamic stresses, secreted autacoids, and metabolism of perfused organs. Bodily organs, including transport circuits such as the vasculature, are coupled to information processing systems (the nervous and endocrine systems). Regulatory mechanisms are targets of mathematical modeling.
4. *Complexity* is illustrated by the heart pump, which has a chaotic behavior in the deterministic framework, enabling it to rapidly respond to environmental stimuli. A constant cardiac frequency yields a bad prognosis similar to strong anomalies in the generation and propagation of the cardiac action potential through the nodal tissue, which can engender an anarchic behavior of cardiomyocytes. This property, which is beneficial with respect to the system functioning, becomes a drawback in signal and image processing that involves averaging to enhance the signal-to-noise ratio.

Like any physiological system, the cardiovascular apparatus functions with various length and time scales. Length scales are related to mechanisms that govern the function of the cardiovascular system and its response to a changing environment, from: (1) Cell signaling implicating messengers, receptors, and effectors (nm), such as molecules involved in the excitation–contraction coupling in cardiomyocytes or in the regulation of the vasomotor tone by the couple formed by the endotheliocyte and smooth myocyte. (2) Adapting cells and their organelles (μm). (3) Cell clusters organized in a tissue within an extracellular matrix (mm). (4) Organ, i.e., the cardiac pump or a vascular compartment (cm).

Multiscale modeling is aimed at coupling these different length scales, whereas the major objective of multilevel modeling is to model the entire vascular circuit coupling models of the bloodstream considering three or fewer spatial dimensions. Whereas three-dimensional models describe the field of the hemodynamic variables (flow velocity and stress) in a set of nodes within a mesh obtained from discretization of a continuum, the distributed (one-dimensional) and lumped parameter models (i.e., electrical analogs) are strongly simplified versions of reality.[2]

[2]In a distributed parameter model, a vascular segment is assumed to be a succession of infinitesimally long slices, in which hemodynamic variables are only computed at the vessel axis, the axial tension between slices being neglected. In a lumped parameter model (zero-dimensional model), the simplification increases a step further, as hemodynamic variables are computed in a single node assumed to represent a given vessel between two branching points.

The time scales range from the fast adaptation relying on signaling axes associated with stored molecule release (milliseconds to minutes) up to gene transcription (hours) and adaptive and adverse wall remodeling (e.g., adaptive and adverse cardiac responses to regular exercise and hypertension respectively; i.e., days, weeks, and months). For example, hemodynamic stress-gated ion channel opens in a time of the magnitude order $\mathcal{O}$(ms) and cytosolic calcium (Ca^{2+}) concentration and nitric oxide (NO) release happens in a time $\mathcal{O}$(s). In addition, the cardiovascular apparatus is subjected to the circadian cycle (i.e., a major day–night rhythm related to the sleep–wake cycle and accessory signals, such as food intake and body temperature).

As hemodynamic factors are implicated in vascular diseases via the local stress field (pressure and wall shear stress), impingement force, and residence time of conveyed molecules, mechanical simulations can complement the medical check-up.

Blood Flow

The cardiovascular apparatus comprises two major compartments, the cardiac pump and vasculature. Structurally, the closed cardiovascular circuit includes two subcircuits in a series, the high-pressure systemic and low-pressure pulmonary circulation, blood being propelled in these subcircuits by two apposed pumps enclosed in a single organ, the heart. Blood is conveyed from the right ventricle to the left atrium through the pulmonary circulation, and from the left ventricle to the right atrium through the systemic circulation.

The right and left cardiac pumps expel identical volumetric flow rate at each time of the systole, i.e., during the ejection phase of the cardiac cycle, according to the mass conservation principle.

Blood flows mainly in a single direction from one cardiac pump to the organs and then to the second cardiac pump, despite relatively strong flow reversals in proximal elastic arteries during diastole.

Once ejected from the ventricles, blood circulates down to the capillaries situated within diffusion distances ($\leq 10\,\mu$m) of parenchymal cells. Blood vessels are endowed mainly with capacitance and flow resistance. The capacitance of proximal arteries (close to the cardiac pump) maintains blood flow during diastole. The capacitance of veins adjusts blood volume to the body's needs. Resistance of small distal arteries and arterioles is linked to autoregulatory control that allows the organ to keep perfusion of downstream tissues constant.

Blood pressure is determined by peripheral arterial resistance, stroke volume, and cardiac frequency. Blood pressure changes are sensed by the baroreceptors that influence cardiac frequency via the arterial baroreflex control loop. Conversely, cardiac frequency variations influence blood pressure.

Blood pressure and cardiac frequency variability and baroreflex sensitivity are influenced by genetic factors, in addition to environmental parameters [6]. However, the genotype (genetic defects) may not be related to the phenotype (manifestations of a disorder), as a patient can have a positive genotype for a given trait (a genetic

mutation) without the pathological condition. The transcriptome does not entirely reflect the proteome (i.e., cell- and circumstance-specific output of the genome, especially post-translational modifications).

Among environmental factors, deficiencies or excesses in the content or availability of trace elements (e.g., degree of mineralization of local water supplies) can be involved in chronic cardiovascular diseases [7]. Trace metals (cadmium and lead) contribute to hypertension and atherosclerosis [8].

Gas Transport

The cardiovascular and respiratory circuits are functionally coupled, as they achieve an adequate continuous supply of oxygen and nutrients and adjusted clearance of carbon dioxide and other metabolic wastes produced by the body's cells.

Oxygen and carbon dioxide are carried by blood from the lungs to bodily organs, hence by convection. Both gas species combine with chemical compounds, which increases the transfer amount.

Oxygen and carbon dioxide diffusivity and solubility are important parameters of gas transfer in biological tissues. Diffusion of gas species occurs in gas (e.g., air in pulmonary alveoli), water, gels, and solids, and hence in biological tissues (e.g., alveolocapillary membrane and blood). It occurs because of the gradients of concentrations in air and partial pressures (total mixture pressure multiplied by the gas species fraction) through a biological tissue. The diffusion coefficient ($\mathcal{D}$) is usually about 10^4 times greater in air than in water. It depends on temperature and pressure ($\mathcal{D}(T, p)$); it increases with rising temperature, molecules moving faster, and decreases with augmenting pressure, which compacts molecules and reduces their motion (Table 1). The diffusion coefficient is most often given for a binary mixture, and hence not air, in which the composition of gases varies owing to the added water vapor in airways to the major gas components (nitrogen, oxygen, and carbon dioxide). The diffusivity is generally related to given pairs of gas species in a multispecies mixture.

In fluids at a given temperature, the gas diffusion rate (D_g) depends on the partial pressure difference between the fluid compartments (Δp), cross-sectional area of the diffusion pathway (A), gas solubility ($\mathtt{s}_\mathrm{g}$), diffusion distance (d), and gas molecular mass (m_g) [12]:

$$\mathsf{D}_\mathrm{g} = \frac{\mathtt{s}_\mathrm{g} A \Delta p}{d m_\mathrm{g}^{1/2}}, \tag{1}$$

the gas diffusion coefficient ($\mathcal{D}$) being proportional to the ratio $\mathtt{s}_\mathrm{g}/m_\mathrm{g}^1/2$.[3]

[3]The molecular mass of a substance is the mass of one molecule of the chemical species (air molecular mass of air 28.97, carbon dioxide 44.01, nitrogen 28.02, oxygen 32.0, and water vapor 18.02 kg/kmol).

Table 1 Diffusivities of oxygen and carbon dioxide (Sources: [9–11])

Gas	Diffusivity (m^2/s)
Oxygen diffusivity in blood	
p_{O_2} = 5.3 kPa (40 mmHg) at 37.5 °C	1.51×10^{-9} [9]
p_{O_2} = 13.3 kPa (100 mmHg) at 37.5 °C	1.33×10^{-9}
16 gHb/dl at 38 °C	1.6×10^{-9} [10]
Dissolved carbon dioxide	
In water at 25 °C	2.02×10^{-9} [11]
(dissolved bicarbonate ion: 1.17×10^{-9})	

Table 2 Blood gas partial pressures (kPa [mmHg]) in various compartments

	Atmospheric air	Inspired humidified air	Alveolar air	Pulmonary arterial blood	Mixed venous blood	Expired air
p_{O_2}	21.3 (160)	20.0 (150)	13.3 (100)	13.3 (100)	5.3 (40)	2.1 (16)
p_{CO_2}	0.03 (23)	0.04 (30)	4.8–5.3 (36–40)	5.3 (40) [48 ml/dl]	6.1 (46) [52 ml/dl]	3.6–4.3 (27–32)

The gas transfer rate through a biological tissue is related to Krogh's diffusion. Krogh's gas diffusion constant at a given temperature in a given biological tissue (Kr_g) corresponds to the product of the gas diffusion coefficient and its capacitance (ratio of its concentration to its partial pressure). Fick's law of diffusion, which provides the rate of gas mass transfer per unit time ($\dot{m}$), is then given by:

$$\dot{m} = Kr_g A \Delta p / h, \tag{2}$$

where h is the thickness of the diffusion barrier. At 37 °C, Krogh's diffusion coefficients for oxygen and carbon dioxide in rat skeletal muscle are 1.31 and 28.0 10^{-9} mmol/cm/mn/mmHg, respectively [13].

Oxygen level cascade, i.e., p_{O_2} decrease from inhaled air to the mitochondrion comprises uptake in the lungs, the carrying capacity of blood, delivery to the capillaries, interstitium, and then cells, and the cellular use of oxygen (Table 2; Vol. 6, Chap. 4. Physiology of Ventilation). Large pulmonary veins receive both oxygenated blood from the pulmonary circuit and deoxygenated blood from the systemic bronchial veins (shunt flow). This venous admixture of blood reduces the O_2 partial pressure to 12.6 kPa (95 mmHg) [12].

In the lung, oxygen is added in blood, its partial pressure rising from 5.3 kPa (40 mmHg) to 13.3 kPa (100 mmHg) and simultaneously carbon dioxide is removed, its partial pressure lowering from 6.1 kPa (46 mmHg) to 5.3 kPa (40 mmHg). The transfer rate of carbon dioxide is then greater than the rate necessary to balance the oxygen transfer.

Table 3 Blood gas solubility at 37 °C, solubility rising as the temperature falls

Gas	Solubility (ml/dl/kPa)	Solubility (ml/dl/mmHg)	Solubility (mmol/l/kPa)	Solubility (mmol/l/mmHg)
O_2	0.023	0.003	0.01	0.0013
CO_2	0.52	0.069	0.231	0.0308

The arterial partial pressure of oxygen ($p_{a_{O_2}}$) depends on inspired O_2 concentration, atmospheric pressure, alveolar ventilation, ventilation/perfusion distribution in the lungs, and O_2 diffusion from the alveoli to the pulmonary capillaries.

Over the surface of the pulmonary alveolus, hemoglobin in a solution in red blood capsules binds oxygen (9.2 mmol O_2/l). Oxygen is mainly carried in blood by red blood capsules (97–98%), a small fraction dissolved according to Henry's law[4] ($H_{O_2} \times p_{O_2}$; H_{O_2}: O_2 Henry solubility; Table 3).

- *Oxygen saturation* ($S_{a_{O_2}}$) is the ratio of oxygen linked to hemoglobin with respect to the oxygen capacity (maximal binding amount).
- *Oxygen content* in arterial blood ($C_{a_{O_2}}$) is the sum of O_2 carried on Hb and dissolved in plasma:

$$C_{a_{O_2}} = S_{a_{O_2}} \times [Hb] \times 1.34 + p_{O_2} \times 0.003 = 19.4 + 0.3 \sim 20\,\text{ml/dl}. \quad (3)$$

  The amount of oxygen bound to completely saturated hemoglobin, i.e., the theoretical maximal oxygen carrying capacity, is 1.39 ml/g Hb, but measurement gives a capacity of 1.34 ml O_2/g Hb.
- *Oxygen delivery* (D_{O_2} [ml/mn]), which depends on the blood flow rate (q)

$$D_{O_2} = q \times C_{a_{O_2}}, \quad (4)$$

  ranges from 0.9 to 1.1 l/mn.
- *Oxygen consumption* ($\dot{V}_{O_2}$ [ml/mn]) is the amount of oxygen extracted by cells during one minute:

$$\dot{V}_{O_2} = q(C_{a_{O_2}} - C_{v_{O_2}}). \quad (5)$$

  It ranges from 200 to 300 ml/mn.
- *Oxygen extraction ratio*, an index of efficiency of O_2 transport, is the amount of oxygen extracted by cells divided by the amount delivered to cells.

Oxygen is delivered from lungs to cells, blood flowing preferentially to organs where the metabolic activity and hence oxygen demand are greater owing to *hypoxic vasodilation*.

[4]The concentration of a solute gas in a solution is directly proportional to its partial pressure above the solution, when concentration and partial pressure are relatively low (i.e., ideal dilute solution).

Carbon dioxide is produced by cell metabolism in mitochondria. The amount produced depends on the rate of metabolism and relative amounts of metabolized carbohydrates, lipids, and proteins (~200 ml/mn at rest and eating a mixed diet for a respiratory quotient of 0.8) [14].[5]

Carbon dioxide eliminated from cells is dissolved in plasma, as it is more soluble (20-times) than oxygen (~5–7%; s_{CO_2} 0.231 mmol/l/kPa [0.0308 mmol/l/mmHg; corresponding to 0.5 ml/kPa CO_2 in 1 dl blood at 37 °C (s_{CO_2} = 0.069 ml/dl/mmHg)] at 37 °C), binds to plasmatic proteins, particularly hemoglobin as carbamate (carbaminoHb; ~10%), and is carried as bicarbonate ion, the bicarbonate buffer being the most efficient carrier in blood.[6] Approximately 75% of carbon dioxide is carried in red blood capsules and 25% in plasma. Carbon dioxide then returns to the pulmonary alveolus, where it is released and exhaled. The percentage of the total carbon dioxide carried in each form and percentage exhaled from them differ: 5% of dissolved CO_2 in solution and 10% tethered to proteins supplies 10 and 30% of exhaled CO_2 amount respectively [14].

Chemoreceptors transduce a chemical signal into an action potential. The peripheral chemoreceptors, i.e., sensors of the peripheral nervous system in arterial walls, the carotid and aortic chemosensory bodies, and central ones, the chemosensory medullary neurons, primarily regulate breathing to maintain the partial pressures of gases (oxygen and carbon dioxide [$p_{a_{O_2}}$ and $p_{a_{CO_2}}$]) in addition to hydrogen ion concentration (pH) in the arterial blood within normal ranges, adapting the chemoreceptor firing rate.

Chemoreceptors also influence the cardiovascular apparatus directly via medullary vasomotor centers and indirectly via pulmonary stretch receptors, triggering sympathetic signaling to the heart and vasculature to adapt breathing and vascular resistance and hence blood pressure.

Carotid bodies detect a primarily decreased O_2 level and, to a lesser extent, an elevated CO_2 level and lowered arterial pH; aortic bodies sense arterial blood oxygen and carbon dioxide levels.

In response to hypoxia, the oxygen-sensitive glomus cells of the carotid body, a chemosensory organ at the carotid artery bifurcation, release neurotransmitters that activate the carotid sinus nerve to increase breathing frequency within seconds. The chemoreceptor reflex that is activated by hypoxemia ($p_{a_{O_2}} < 10.6$ kPa [80 mmHg]), hypercapnia ($p_{a_{CO_2}} > 5.3$ kPa [40 mmHg]), and acidosis (pH < 7.4) increases the breathing frequency and tidal volume amplitude.

The carotid body chemoreceptor discharge has a respiratory rhythm. In cats, the carotid chemoreceptor is extremely sensitive to small abrupt changes in p_{CO_2},

[5]The respiratory quotient is the rate of carbon dioxide production divided by the rate of oxygen consumption. A carbohydrate diet gives a quotient of 1 and a fat diet of 0.7 [14].

[6]Carbon dioxide diffuses into the red blood capsule (RBC), where carbonic anhydrase quickly converts it into carbonic acid (H_2CO_3), an unstable intermediate molecule that immediately dissociates into bicarbonate (HCO_3^-) and hydrogen ions (H^+). Hemoglobin binds to H^+, limiting pH shift. The newly synthesized bicarbonate ion is exported from the RBC into the plasma in exchange for a chloride ion.

these changes affecting breathing when they happen at an appropriate point in the respiratory cycle [15]. Both elevated p_{CO_2} and lowered hydrogen carbonate concentration (bicarbonate [HCO_3^-]) change impulse frequency, the chemoreceptor response produced by an elevated p_{CO_2} occurring approximately twice as fast as that due to a decayed [HCO_3^-]. In transient changes in p_{CO_2} or pH, the effect of p_{CO_2} may dominate.

In cats, the response curve of carotid body chemoreceptors to lowered p_{aO_2} is hyperbolic, with a frequency of nerve impulses that first decreases rapidly when p_{aO_2} rises and then more slowly from a variable value according to the chemoreceptor unit and hence the nerve fibers (mean25.3 $\pm$ 5.3 kPa [190 $\pm$ 40 mmHg) [16]. The discharge of a single chemoreceptor afferent fiber augments both with increasing p_{aCO_2} at constant p_{aO_2} and pH and with elevating arterial H^+ concentration at constant p_{aO_2} and p_{aCO_2}.

In rodents, the acute response to hypoxia is linked to the olfactory G-protein-coupled receptor, OlfR78, which is highly and selectively expressed in oxygen-sensitive glomus cells and acts as an oxygen sensor [17]. The metabolite lactate, concentrations of which rapidly rise in blood during hypoxia, provokes hyperventilation. It binds to and activates OlfR78, thereby enabling glomus cells to detect hypoxia and stimulate breathing. Activated OlfR78 releases calcium from intracellular stores and causes calcium transients in glomus cells.

Blood gas and hydrogen ion control, and hence control of breathing, relies primarily on the ability of the brain to sense CO_2 and/or H^+ levels, rather than oxygen sensing. *Central chemosensitivity* refers to a change in ventilation attributable to changes in levels of CO_2 and H^+ detected within the brain.

The central chemoreceptors of the ventral medulla oblongata monitor CO_2 level in the cerebrospinal fluid, as chemoreceptor neurons contain processes that can provide access to the cerebrospinal fluid circuit more efficiently than to penetrating branches of the brain vasculature. In addition, glial cells participate in the pH regulation of interstitial and cerebrospinal fluid. In the cerebrospinal fluid, pH is regulated by transport mechanisms through the capillary endothelium in the choroid plexus and blood–brain barrier, and by p_{CO_2} changes associated with breathing and cerebral blood flow. Neuronal and glial processes close to blood vessels may detect changes in blood pH, hence minimizing the influence of the blood–brain barrier, which controls ion transfer.

The central chemoreceptors in the brainstem protect against rapid changes in pH in the blood. In fact, central chemoreceptors are responsive to interstitial fluid pH in the brain.

Many regions participate in central chemoreception, such as the brainstem, cerebellum, hypothalamus, and midbrain [18]. They sense H^+ concentration in the cerebral interstitial fluid and detect and integrate information from: (1) Alveolar ventilation via arterial p_{aCO_2} (2) Cerebral blood flow and metabolism (3) Hydrogen ion control They then influence breathing, airway resistance, and blood pressure via the sympathetic nervous system.

Chemoreception, sleep, and wakefulness depend on various cerebral regions that include Tac_1+[7] Phox2b+ neurons in the retrotrapezoid nucleus, serotonergic neurons of the medullary raphe, neurons of the caudal ventrolateral medulla, neurons of the dorsal respiratory group in the nucleus tractus solitarius, hypothalamic orexin+ neurons, in addition to neurons of the locus ceruleus in the dorsal pons; of the rostral region of the fastigial nucleus, a deep cerebellar nucleus; and of the rostral ventral respiratory group, the pre-Bötzinger complex [18]. The retrotrapezoid nucleus and medullary raphe in the ventral medulla are two interacting chemoreceptor areas, the caudal medullary raphe amplifying the response to CO_2 at the retrotrapezoid nucleus. In wakefulness (but not during NREM sleep), orexinergic neurons signal to the retrotrapezoid nucleus and rostral medullary raphe, thereby enhancing the responses from the carotid body, retrotrapezoid nucleus, caudal nucleus tractus solitarius, caudal ventral medulla, and likely the locus ceruleus [18].

In cats, medullary extracellular fluid pH changes within seconds following an acute modification of alveolar and arterial p_{CO_2} [19]. The respiratory response inversely matches changes in the pH of the extracellular medium, but not in the cerebrospinal fluid. The relation between increasing end-tidal p_{CO_2} upon airway occlusion and medullary hydrogen ion concentration is linear, but not that relating $[H^+]$ in the extracellular space to the respiratory response.

The central respiratory chemosensitivity depends on two types of plasmalemmal proteins, the pH-sensitive TASK2 channel and proton-activated G-protein-coupled receptor GPR4 on chemosensory neurons of the mouse retrotrapezoid nucleus [20]. Regulation of breathing by CO_2 relies on GPR4 (or GPR19), which senses the blood level of protons generated from carbonic acid. The ventilatory response to CO_2 involves the K^+ TASK2 channel ($K_{2P}5$). Hence, the control of breathing depends on the GPR4 that works with TASK2 on chemosensory neurons.

Central and peripheral chemoreceptors cooperate. At least in rats, carotid afferents synapse at nucleus tractus solitarius neurons, which communicate directly with those of the retrotrapezoid nucleus [18]. Moreover, the carotid bodies raise the ventilatory response to central p_{CO_2}, demonstrating the potent interaction between central and peripheral chemoreceptors.

Central and peripheral chemoreceptors also participate in maintaining pH homeostasis. Metabolic acidosis stimulates ventilation via peripheral and central chemoreceptors to lower $p_{a_{CO_2}}$ and $[H^+]$.

The sympathetic nervous system also regulates activity of the heart as well as small arteries and arterioles responsible for the systemic vascular resistance, thereby controlling blood pressure. The sympathetic output is governed by many central and peripheral mechanisms, especially the baroreflex (baroreceptor-triggered reflex), the fastest mechanism that regulates acute arterial pressure changes via the cardiac

[7] Tachykinin receptor-1.

frequency and contractility in addition to vasomotor tone and hence peripheral resistance.[8]

Yet, increased ventilatory output raises sympathetic nerve activity via pre-sympathetic neurons of the rostral ventrolateral medulla and likely GABAergic neurons of the caudal ventrolateral medulla (CO_2-sensitive respirophasic change in sympathetic nerve activity) [18]. In addition, hypercapnia engenders tonic CO_2-sensitive activity independently of respiratory events. With increased CO_2 levels, sympathetic discharge, phrenic nerve activity, and blood pressure heighten. The p_{aCO_2} threshold for the pressor sympathetic response equals approximately 4.8 kPa (36 mmHg) and that for the phrenic nerve is about 5.8 kPa (44 mmHg) [18].

Catecholaminergic neurons of the brainstem project in the forebrain, hindbrain, and spinal cord to many regions implicated in the control of respiratory and cardiovascular function, hence modulating these functions [21]. Excitatory noradrenergic neurons of the A6 group maintain breathing frequency, whereas A5 neurons slow breathing and cardiac frequencies. Lesions of A2, A3, A5, and A6 neurons attenuate blood pressure. Orexin neurons that innervate the pre-sympathetic neurons of the rostral ventrolateral medulla can increase sympathetic nerve activity. In mice, orexin depletion diminishes blood pressure in wakefulness [18].

Carbon dioxide combines with water to form carbonic acid (H_2CO_3), which dissociates in water into HCO_3^- and H^+ ions. An increase in blood H^+ concentration of only 100 nmol/l (i.e., a decrease of 0.1 unit of pH) can be fatal. Hence, regulated excretion of CO_2 by breathing is an essential life-preserving process. In rodents, hypercapnia-primed release of ATP from the chemosensory areas at the ventral surface of the medulla is crucial for breathing regulation. In humans, p_{aCO_2} is regulated around a set point of 5.3 kPa (40 mmHg). Connexin-26, which constitutes hemichannels and gap junctions, is a CO_2 sensor; CO_2 binds to the Cx26-formed hemichannel, which then opens and releases ATP, thereby contributing to the CO_2-dependent regulation of breathing [22]. In humans, a mutation that removes CO_2 sensitivity of Cx26 reduces respiratory drive and causes periods of central apnea.

At the cellular level, oxygen is the final electron acceptor during oxidative phosphorylation. Immediately, hypoxia suppresses ATP consumption and hence major ATP sinks in the cell, i.e., protein translation and ion channel activity. During a rescue phase, transcription of hypoxia-responsive genes increases; these

[8]The cardiopulmonary region of the body is innervated by multiple types of sensors and mechano- and chemosensitive nerves. Baroreceptors are mechanoreceptors located in the carotid sinus and aortic arch that sense arterial pressure changes and tension in the arterial wall and react. Impulses sent from activated aortic and carotid baroreceptors are transmitted to afferent vagal and glossopharyngeal nerves and then to the nucleus of the tractus solitarius and vasomotor center of the brainstem. Acute hypertension stretches the baroreceptors, which increase their impulse firing rate, decreasing sympathetic signaling and increasing parasympathetic vagal tone. Conversely, a sudden hypotension diminishes wall tension and hence the firing rate, stimulating sympathetic activity in the heart (cardiomyocytes and nodal cells, especially those of the sinusal node), and blood vessels and inhibiting vagal tone.

genes encode proteins involved in glucose transport, glycolysis, erythropoiesis, angiogenesis, vasodilation, and respiratory rate to minimize the effects of hypoxia.

Adaptation to hypoxia relies on the stabilization of *hypoxia-inducible factors* (HIF). Hypoxia-inducible factors are oxygen-sensitive heterodimeric transcription factors of the basic helix–loop–helix (bHLH) superfamily that control the long-term response to hypoxia. The HIF dimer consists of an oxygen sensor (HIF1α–HIF3α) and a constitutively expressed subunit HIF1β. Its activity is regulated by post-translational modifications.

Hypoxia-inducible factors trigger transcription of genes that facilitate adaptation to hypoxia and survival of cells in cooperation with transcriptional coactivators. Hypoxia-inducible factor-1 enhances glycolysis and attenuates oxidative phosphorylation and hence metabolic dependence on molecular oxygen for ATP synthesis. In hypoxia, the shift from oxidative phosphorylation to glycolysis decreases the generation of ROS.

Hemoglobin functions not only as a carrier of proper amounts of oxygen to cells, but also as a sensor and transducer that detect the local oxygen content and convey oxygen-responsive NO, thereby regulating the vasomotor tone.

Modeling

The *golden number* (also dubbed golden ratio, proportion, mean, or section) equals 1.618034, i.e., $(5^{1/2} + 1)/2$. This irrational number can be defined by a special geometric construction, for example dividing a line into two segments, the ratio of the longer (a) to the smaller segment (b) equaling that of the whole length to the longer segment ($a/b = (a + b)/a$).[9] It is denoted by the Greek letter φ, honoring the name of the Greek sculptor, painter, and architect Phidias (−480 to −430), who employed it extensively.

In Leonardo da Vinci's drawings of the human body (Vitruvian Man [∼1490]), depicting a body in a standing position inscribed in a square and then with feet and arms outspread inscribed in a circle, the ratio of the foot–umbilicus (navel) distance to umbilicus–head top is approximately the golden ratio.

The ratio of two successive Fibonacci numbers (x_i/x_{i-1}) is very close to the golden ratio, especially after the couple (21, 13).[10]

Let us consider the following quantities: arterial diastolic (DBP), systolic (SBP), and pulse pressure (PP), in addition to cardiac period (T) and systolic (SD ∼ 0.38 T) and diastolic duration (DD ∼ 0.62 T). The cardiac cycle phase duration ratios

[9]The ratio of the circumference of a circle to its diameter, $\pi = 3.141593$, is another irrational number.

[10]The Fibonacci sequence is the series of numbers starting from 0 and 1 in which the next number is calculated by the sum of its two previous numbers ($x_{i+1} = x_i + x_{i-1}$; 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, etc.), every ith Fibonacci number being a multiple of x_i.

SD/DD and T/DD are nearly equal to the golden number. With the arterial pressure value triplet (16.0, 10.6, and 5.3 kPa [120, 80, and 40 mmHg]), the ratios DBP/PP and SBP/DBP are equal to 2 and 1.5 respectively, whereas with the triplet (16.0, 9.8, and 6.1 kPa [120, 74, and 46 mmHg]), these ratios are nearly equal to the golden number [23].

The golden number, which describes two measures of any kind, can be used for simple modeling, which cannot usually be applied in natural sciences. Modeling in biology, physiology, and pathophysiology is associated with ordinary (ODEs) and/or partial differential equations (PDEs), PDEs usually being linked to a higher degree of abstraction.

For example, active energy-consuming materials immersed in a fluid or a gel move and alter the properties of their environment. They are endowed with self-propulsion, converting chemical energy into mechanical energy. Cell motility is represented by a hierarchy of PDE-based models. The classic equation set was proposed by C. S. Patlak in 1953 and E. F. Keller and L. A. Segel in 1970 [24]. Cell chemotaxis is modeled by a set of parabolic and elliptic equations that take into account only the cell density $n(\mathbf{x}, t)$ and concentration $c(\mathbf{x}, t)$ of chemoattractant released by cells, which immediately diffuses, using a set of parameters including a constant chemotactic sensitivity (S_{ca}) and cell ($\mathcal{D}_c$) and chemoattractant diffusivity ($\mathcal{D}_{ca}$), cell proliferation rate (P), and chemoattractant production (P_{ca}) and degradation rate (D):

$$\frac{\partial n}{\partial t} = \mathcal{D}_c \nabla^2 n - \nabla \cdot (n \mathsf{S}_{ca} \nabla c) + \mathsf{P} n, \tag{6}$$

$$\frac{\partial c}{\partial t} = \mathcal{D}_{ca} \nabla^2 c + \mathsf{P}_{ca} n - \mathsf{D} c, \tag{7}$$

According to the Blanchet–Dolbeault–Perthame theorem in $\mathbb{R}^2$ [25], given the initial mass ($m_0 = \int_{\mathbb{R}^2} n_0(x)\, dx$),

1. If $\int_{\mathbb{R}^2} |x|^2 n_0(x) dx < \infty$
2. When $m_0 > \dfrac{8\pi}{\mathsf{S}_{ca}}$, then the Keller–Segel system blows-up in finite time
3. When $m_0 < \dfrac{8\pi}{\mathsf{S}_{ca}}$ and $\int_{\mathbb{R}^2} n_0(x) |\log(n_0(x))| dx < \infty$, then a weak solution exists

Modeling is aimed at enhancing knowledge and an understanding of natural processes, predicting, assessing quantities and parameters that cannot be directly measured, creating new hypotheses and paradigms, and redesigning models and theories according to outcomes, thereby driving rather than complementing investigations.

However, this simplification of the reality is a falsification. *Verification* is aimed at proving that the equations of the mathematical model are solved correctly. *Validation* is aimed at comparing the solution obtained using the selected model with measurements to check the validity of numerical tests. Furthermore, systematic truncation error testing and accuracy estimation should be addressed.

> Il y a un imbécile en moi, et il faut que je profite de ses fautes... C'est une éternelle bataille contre les lacunes, les oublis, les dispersions, les coups de vent.[I host a dunderhead, and I need to benefit from his mistakes... This is an eternal battle against gaps, omissions, dispersions, and gales.](Paul Valéry [1871–1945]) [26]

Physiological and pathological processes can be explored using simple physical, mathematical, and numerical models to better comprehend and explain the nature and its patterns. All involved elements must be carefully pondered according to their function and the spatial and temporal scales. The biological complexity is then omitted and the process modeled in a given theoretical context, knowing the sources of errors and handling definitions, concepts, paradigms, and theories underlying the explored process. Usually, the model design needs to be adjusted and measurements and/or the solving procedure to be optimized and adapted to the evolving process.

Natural complex processes operate at different length and time scales. Multiscale modeling is aimed at representing physiological and pathological phenomena across the biological continuum, i.e., from atoms, molecules, and molecular complexes (nanoscale), to subcellular compartments, cells, and cell clusters (microscale), to tissues (mesoscale), and organs and physiological apparatus (macroscale). Its objective is to describe mechanisms and, coupled with bioinformatics, to predict the occurrence of certain diseases in a given fraction of the population.

Cellular and tissular organization, homeostasis, adaptation, control, and remodeling are not described by mathematical theories of optimal structure–function relations, as general quantities measuring the complex cell behavior are lacking. Adaptive and regulated cellular and tissular components cannot be isolated without missing the integrated function of the entire structure. In addition, chemical activities underlying the structure–function relations obey various rhythms governed by biological clocks. Hence, even in the absence of major changes in cell fate (e.g., growth, division, differentiation, and death), molecules are not only subjected to a constant turnover with given synthesis and degradation rates, but also their concentrations fluctuate in time.

Nevertheless, mathematical modeling based on ODEs or PDEs is used to predict and redesign experiments for a deeper understanding of regulated cellular and tissular processes, such as angio- and organogenesis (implicating cell migration, proliferation, and death) and tissular growth that rely on chemical, physical, and mechanical agents, in addition to remodeling, healing, and repair, keeping in mind that mathematical descriptions afford neither quantitative analyses nor complete solutions and explanations.

> Ce qui est simple est toujours faux. Ce qui ne l'est pas est inutilisable. [What is simple is always false. What is not is unusable.(Paul Valéry) [27]

Any volume in the series "Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems" is aimed at describing physiological and pathophysiological processes to focus on proper mechanisms and carry out adequate modeling, highlighting the major signaling cascades, when they are known. Cells sense any change in their environment, integrate diverse signal sources, and respond to them by the release of material, gene transcription, metabolic adjustment, and adaptive fate.

Signaling pathways can be targets of mathematical representations. They often comprise ubiquitous building blocks, such as the MAPK module, monomeric (small GTPases) and trimeric GTPases (G proteins) linked to their regulators, processed plasmalemmal lipids such as phosphatidylinositols that can engender second messengers. Once they are liganded or, for some, activated by mechanical stress, receptors change their conformation from inactive to susceptible and then active form and transfer signal, actuating intracellular pathways using a set of adaptors and recruiters.

Most models of reaction sets use a deterministic continuous approach based on rate equations for concentrations of involved substances and complexes described by chemical kinetic models and represented by a set of ODEs, the spatial distribution of compounds being described using compartments.

The rate of each chemical reaction or interaction is based on concentrations of the reacting or interacting chemical species (*rate law*), which is associated with a positive or negative term in the conservation equations, according to the conserved species generated or consumed, elementary reactions being formulated mathematically by the law of mass action.

On the other hand, dynamics in a continuous space can be linked to relatively large concentration gradients. Concentrations are then considered to be functions of both time and space and the process is governed by PDEs. Indeed, outcome depends on magnitude, timing, and spatial localization of signals. Fluxes of the chemical species involved then depend on convection and diffusion in the presence of a pressure and concentration gradient respectively.

Metabolic activities incorporate molecular concentrations and rates of synthesis, transport, molecular interactions, enzymatic transformations involving donors, acceptors, and products, and clearance, in addition to relaxation times (time required for a quantity to reach a new steady state after a disturbance) and regulation by negative and positive feedbacks. Cellular metabolism can be described by time and space scales according to displacements of the molecular species involved, and fluctuations of their concentrations owing to biological rhythms, weak and strong molecular coupling, referring to nonspecific and specific molecular interactions and control.

Cell growth and proliferation depend on tissue perfusion and hence capillary density, uptake of nutrients, and controlled production of the required molecules (sugars, lipids, and proteins) in addition to regulators. The rate of change in cell density is given by birth (division and differentiation), transfer (convection, diffusion, and migration [taxis]), and loss (death) terms, which hinge on various types of stimuli, including growth factors and mechanical stresses, along with matrix properties (composition, organization, component density, and rheology). It is coupled with feeding, i.e., the rate of change in concentrations of nutrients (i.e., production, flux, reaction, and decay).

Mathematical modeling targets maladaptive tissue growth, which causes mural pathological conditions, especially in the heart (hypertension-initiated cardiac hypertrophy) and arteries (atherosclerosis), or results from medical device implantation. Modeling is aimed at improving the clinical strategy.

Tissular remodeling can be investigated on a macroscopic scale and all micro- and mesoscopic scale phenomena lumped in parameters, which are incorporated into a system of nonlinear, coupled, parametric, partial differential equations. This type of equation set is used in continuous-type models that rely on mixture theory. However, this solving procedure necessitates an efficient identification stage to estimate the parameters involved.

Vascular wall remodeling is usually supposed to depend on the wall shear stress sensed by endotheliocytes on their wetted (luminal) surface and intramural circumferential and axial tension detected by smooth myocytes and fibroblasts, stretch and parietal shear playing a minor role on endotheliocytes and smooth myocytes respectively. Wall shear stress affects cell proliferation, apoptosis, and migration in addition to matrix deposition and re-organization via gene expression.

Numerical simulations can be aimed at optimizing a drug dose for a given patient and administration time using pharmacokinetics–pharmacodynamics (PK–PD) models. These models describe the evolution of the drug concentration that circulates in the blood for a given dose and administration mode and link between the blood drug concentration and the magnitude of the drug's effect. The objective is to predict the optimal time of drug re-administration and dose, hence guaranteeing the drug's desired action, but minimizing side effects. This problem is related to optimal control. The model must take into account interindividual variability.

Mechanical Investigations

The main components of biological tissues, cells, and matrix can be considered as a material that experiences fluidization–gelification cycles according to the stress field applied. The cytoplasm and extracellular medium contain filaments and fibers, actin and myosin, microtubules, and intermediate filaments in the intracellular medium, collagen, and elastin fibers in the matrix, in addition to relatively large particles, cellular organelles, and cells respectively.

Biomechanics, i.e., continuum mechanics applied to physiology, deals with the mechanical behavior of biological fluids (e.g., air and blood) and solids (conduits and organs). Biomechanical methodology is based on computational models and experimental circuits that integrate the structure and function of the explored organ, the physical properties of which can be defined by continuous functions.

Modeling obeys geometrical and dynamical similarity, i.e., keeps the values of ratios between calibers and lengths along with dimensionless parameters (e.g., Reynolds and Strouhal numbers), which are ratios of forces, and governs length and time scales.

The objective of biomechanical works is to assess the function of a selected compartment of the cardiovascular circuit, such as the cardiac pump or a vascular segment, with or without branchings. This compartment is characterized by its morphology (shape); geometry (size); structure (tissue composition); rheology (mechanical properties), with given pre-stresses (axial and circumferential residual

tension); and values of the flow governing parameters, under normal and pathological conditions. For example, in hypertension, which is associated with altered cell and matrix mechanics and dysregulated mechanotransduction, the vascular wall stiffens.

Physical phenomena employ a set of quantities (e.g., mass, temperature, pressure, velocity, and energy). The goal of biomechanical modeling is to predict the fields of the physical variables involved by solving well-posed boundary value problems associated with the balance laws of mechanics (e.g., the conservation of mass, momentum, and energy) in a given context. Moreover, once the numerical procedure is verified and the solution validated, the role played by a given parameter can be easily tested, the others remaining constant.

Multilevel models couple three-dimensional compartments (3D) of the cardiovascular circuit to one-dimensional (1D or distributed parameter models) and lumped parameter models (0D models or electrical analogs) of other compartments of the circuit. Coupling of 3D, 1D, and 0D models enables the vascular network with its upstream and downstream impedances to be incorporated.

The unsteady 3D developing flow of viscous incompressible blood through a segment of the vascular circuit under pathological conditions can be described by the Navier–Stokes equations derived from the theory of continuum mechanics. This equation set predicts flow behavior for given initial and boundary conditions (i.e., input and output impedances) and the values of flow governing dimensionless parameters, which control the local flow dynamics, in a given rigid or deformable computational domain derived from medical images.

The Navier–Stokes equations describe the flows of fluid particles that can be conveyed through deformable curved conduits of complicated configuration. Three-dimensional models provide the entire flow field (intraluminal pressure and shear stress, mural stress, and velocity, in addition to its derived variables such as vorticity), more precisely in a set of nodes separated by a discretization scale (space step). The higher the node number, the closer the computational domain is to the continuum. However, solving is computationally expensive, especially when dealing with time-dependent blood–vessel wall interaction. They are then used to explore a segment of the anatomical circuit and are sensitive to boundary conditions.

The simplest lumped parameter models assume that all the properties (mainly resistance and compliance) of the blood vessel can be concentrated in a single point. Each duct of a network is then represented by a single node. This approximation amounts to using electrical analogs, i.e., considering linearization. Hence, many effects, nonlinear convective acceleration, kinetic energy effects due to duct geometry changes and branchings, wave propagation, and large displacements are neglected.

Modeling of pulse wave propagation generally relies on distributed parameter models that are based on mass and momentum conservation integrated over the cross-sectional area of the explored vascular segments. The underlying hypothesis is that all flow features (transmural pressure, luminal cross-sectional area, and fluid velocity) in any vessel segment of infinitesimal length can be assumed to be uniform; they are integrated in a single point at the vessel axis. Therefore, the

vessel is assumed to be a continuous set of infinitesimal thickness slices, which interact via the flow dynamics coupled with the wall mechanics, but without mural connection between the selected sections (or stations), as axial tension exerted by the deformation of a cross section by a traveling wave to its apposed stations is omitted. Each conduit is then represented by a set of nodes separated by an infinitesimal length.

Modeling pulse wave propagation in the arterial tree in diseases requires the vessel law, which relates the cross-sectional area (A) to the transmural pressure (p). The simplest numerical procedure is based on finite differences and the method of characteristics, when the flow remains subcritical. However, in diseases, the vessel law must be investigated.

Adequate simulations of multiphysics problems rely on solver-coupling platforms. Physiological ducts have deformable walls with a given rheology under given dynamical conditions.

Solid media are most often heterogeneous, multidomain-containing viscoelastic continua. They are described by the constitutive equation that relates stress (i.e., force per unit area), strain (a dimensionless change in configuration), and rate of deformation. These quantities are mathematically defined by symmetrical tensors, i.e., nine component elements ($T_{i,j}$, i, $j = 1, 2, 3$; i, row index corresponding to the plane on which the stress is exerted; j, column index corresponding to the direction of stress according to coordinate axes) in the three-dimensional space; they can be represented by a 3×3 symmetrical matrices in the absence of external moments.

The fundamental behavior of material, which is determined by time-independent and -dependent tests (e.g., cyclic and multi-axial loading and test at constant stress [creep test] and at constant strain [relaxation test]), is commonly represented by elementary mechanical features and models.

- An elastic body is modeled by a spring. Most materials can be assumed to obey the elasticity law at a low level of strain. The stress (applied load) is related to the strain (deformation) using the stiffness coefficient (elasticity modulus) for axial loading (compression and tension in a given direction, i.e., in general, one of the main axes of the body) and the shear modulus for shear (torsion and bending, i.e., forces acting in a tangential or transverse direction with respect to the surface and major axis of the body respectively). These moduli expresses the resistance to deformation. Compliance is the inverse of the elasticity modulus. Stress and strain are in phase. The body's configuration returns to its original shape when the applied stress is removed.
- Viscosity is represented by a dashpot. The stress is related to the speed of strain (deformation rate) using the viscosity coefficient, which also expresses the resistance to deformation. The faster the strain rate, the greater the stress. Stress and strain are shifted from each other. The resistance to deformation is the strongest when the deformation rate is the smallest for a given load.
- Plasticity corresponds to the behavior of a friction element.
- In addition, intermediate behaviors can be observed (e.g., viscoelasticity [i.e., materials such as biological tissues behaving as a combination of viscous and elastic components] and viscoplasticity).

The strain energy function relates stress to strain in a hyperelastic material such as vessel walls. The partial derivatives of the strain energy function with respect to Green's strain components are related to the second Piola–Kirchhoff stresses. The strain energy function can be determined by solving an inverse problem based on experimental data.

The influence of perivascular support from the surrounding tissue is generally neglected. However, some vessels are more constrained than others (e.g., distinct environments for epicardial and intramural coronary arteries). A radial constraint increases the radial stress, but decreases the longitudinal and circumferential stresses [28].

The nonlinear pressure–cross-sectional area relation, which couples blood dynamics to the vascular wall mechanics, yields the compliance of the explored vessel (slope at a given pressure $\complement[p]$). In an unsteady flow, other important quantities include the mean circumferential stress $c_\theta = pR_\mathrm{h}/2h$ (p: blood pressure; R_h: hydraulic radius; h: wall thickness) for a thin-walled ($h \ll R$) cylindrical pressurized vessel (Laplace–Young equation) and characteristic impedance $\rho c/A$ (ρ: blood density; c wave speed in the blood vessel; and A: cross-sectional area).

Four pre-requisites of any problem in biomechanics include: (1) Achievement of the computational domain, i.e., personalized geometry, with its given structure based on anatomical and histological data (2) Determination of the material constants of the body of interest or of each subdomain in the case of a composite material according to available rheological results, if possible, obtained properly in vivo (3) Selection of the equation set associated with the problem based on the governing physical laws, depending on assumptions (4) Definition of the appropriate initial and boundary conditions that incorporate the constraints of the neighborhood

Medical signal and image processing provide the three-dimensional domain of interest for numerical simulations. Image data are characterized by image quality (contrast, edge quality, artifacts) with a given temporal and spatial resolution and noise level. Segmentation of organs and vessels refers to their separation from each other and the background. Three-dimensional reconstruction of their surfaces is followed by adapted meshing with coarsening and refinement of some regions (e.g., in the core flow area centered around the local vessel axis and in the layer close to the wall respectively). A mesh must be adaptive when coping with evolving processes.

Meshes are then used for computational mechanics, in particular, fluid dynamics. Numerical results are influenced by geometry accuracy, i.e., the quality of image acquisition and processing, mesh design (numbers of mesh nodes and computational cell size, near-wall refined mesh, etc.), boundary conditions associated with the set of differential equations to solve (e.g., simple traction-free conditions [without tangential component of the local stress tensor [$\mathbf{T}$]) at outlets[11] or loose or strong

[11] The traction vector $\mathbf{t}$ is defined as the scalar product of $\mathbf{T}$ and the unit normal $\mathbf{n}$ to the surface of interest. The surface is said to be tractionless if $\mathbf{t} = \mathbf{T} \cdot \mathbf{n} = 0$. In a Newtonian fluid, the stress tensor is given by: $\mathbf{T} = -p\mathbf{I} + 2\mu\mathbf{D}$, where $\mathbf{D}$ is the rate of deformation tensor and $\mathbf{I}$ the unit tensor.

coupling with distributed and/or lumped parameter models of the remaining part of the circulatory circuit), control parameters (time and space steps), and simulation factors (fluid properties, flow governing parameters, and blood and vascular wall rheology).

Computed values have an intrinsic uncertainty due to assumptions, approximations, and errors linked to the geometrical reconstruction, meshing procedure, physical modeling, and mathematical and computational methods.

However, some features (e.g., material constants and, in the case of cardiac mechanics, the subject-dependent orientation of myofibers within the different myocardial layers across the heart wall), pressure and/or velocity boundary conditions, and variables (impedance of various involved vascular segments) of lumped parameter models, even when they are obtained in vivo, are often taken from different individuals, as proper measurements are tedious and hence cannot be carried out systematically in every subject.

Medical devices are substitutes for defective organs. They include sensors that gather information on the patient state, physiological variables following a circadian rhythm, and, depending on the subject, an actuator that acts on the body, and a control algorithm that enables the decision of the action to be achieved. Another goal of implantable devices is to restitute the caliber of a narrowed conduit and to obviate a secondary narrowing. The shape of implantable devices can be adapted to the patient's anatomy using shape optimization-based modeling.

Book Series

Whereas volume 7 of the series "Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems" was devoted to the cardiac pump and genesis of cardiopathies from a modeling perspective rather than a clinical point of view, volumes 8 to 13 primarily focus on diseases of the vasculature. They are aimed at presenting the processes and agents involved to adequately model some aspects of vasculopathies. Volumes 8 and 12 set the stage, i.e., yield pathophysiological elements implicated from the intracellular to the tissular level. Volume 13 describes major vasculopathies that are studied by mathematical and mechanical approaches.

Volume 8 presents the clinical field of vasculopathies, i.e., cardiovascular markers and risk factors, focusing on hypertension, hyperglycemia and diabetes, hyperlipidemias and obesity, behavioral risk factors, and the genetic framework.

Volume 9 presents the individual context, i.e., medical history with the favoring circumstances (aging, ciliopathies, and anomalies of the respiratory tract). It explores cell responses to various types of stressors such as hypoxia, how its cellular organelles involved in quality control manage stress more or less efficiently, and describes cell autophagy and different types of cellular death, which are normal phenomena that can be exacerbated under some circumstances.

Volume 10 updates the data on vascular wall structure and architecture and reviews the genesis of new circuits in the arterial tree of the human adult and

arteriogenesis, i.e., the development of collaterals. It also describes processes implicated in adverse wall remodeling.

Volume 11 gives the molecular context within the cell, i.e., epigenomic factors, regulatory RNAs, lipids and lipoproteins, reactive oxygen and nitrogen species, gaseous messengers, as their deficiencies, excessive production, and dysregulated activity disturb the body's homeostasis.

Endothelial dysfunction and chronic vascular inflammation, which generally yield the framework of cardiovascular disease, in addition to the metabolic syndrome, the consequence of an imbalance between caloric intake and energy consumption, thrombosis, and lymphedema, are studied in volume 12.

Volume 13 focuses on major diseases of the vasculature that are targets of mechanical and mathematical investigations, especially atherosclerosis and aneurysms.

Lung diseases constitute the content of volume 14. It includes respiratory infections and allergies and obstructive and restrictive disorders.

The main mechanical concepts and parameters, starting from a brief introduction of historical findings for a fast understanding are introduced in volume 15. Physical principles govern living organs and physiological apparatuses. Physical phenomena employ a set of quantities (e.g., mass, temperature, pressure, velocity, and energy). Mechanical concepts are used not only in mechanical modeling, but also in theoretical aspects of biology and medical practice. In particular, the Navier–Stokes equations describe flows of fluid particles. In general, physiological fluids are conveyed through deformable curved conduits of complicated configuration. Mechanical modeling is aimed not only at predicting the fields of the physical variables and testing the effect of the parameters involved, keeping all other quantities constant, but also at solving inverse problems, thereby enabling physiological quantities that cannot be directly measured to be assessed. Volume 15 contains chapters devoted to hemodynamics, air transport, aerosols, and rheology, as walls of the vascular circuit and respiratory tract are deformable and blood is a composite material, this flowing biological tissue carrying gas, nutrients, wastes, and cells to maintain life. It also introduces the methodology, i.e., measurements using physical models and, when ethically possible, in vivo, and numerical simulations, which are becoming a mandatory step in the development of medical devices.

Book Organization

The present book includes seven chapters for handling the biological and clinical framework, which is mandatory for adequate modeling. Chapter 1 briefly introduces major cardiovascular diseases that are potential targets of mathematical and mechanical investigations. Chapter 2 presents cardiovascular risk factors and markers, the search for new criteria being aimed at improving the early detection of chronic diseases. The following chapters focus on: (1) Hypertension (Chap. 3), which involved the kidney among other organs in addition to many agents (2) Hyperglycemia

and diabetes (Chap. 4) (3) Hyperlipidemias and obesity (Chap. 5) (4) Behavior, i.e., altered circadian rhythm, tobacco and alcohol consumption, physical inactivity, and an unhealthy diet; Chap. 6). Chapter 7 is related to the genetic framework of vasculopathies. Among personal and environmental conditions, the genetic ground explains certain pathophysiological processes involved in vasculopathies, such as dyslipidemia and mutations affecting the vasomotor tone.

This treatise is aimed at serving as a vade mecum for scientists who are not specialized in biology, but model physiological and pathological processes. It does not avoid the pitfall of pleasureless concatenation of observations. Collecting data and key relations is yet a mandatory work done during the preliminary stage of any modeling to handle and accurately represent all important mechanisms involved in the explored process before selecting proper parameters, obviating any redundancies and eliminating accessory information.

The main text contains the essential information needed to steer the explored process and to estimate the level of influence of the implicated agents before modeling.

Some biological aspects, which are not mandatory for achieving proper modeling, are not incorporated in these books. Further details and proper citations to original works can be found, especially in review articles.

Any information bears interest only when it is inscribed in the continuity of development. Footnotes are immoderately used throughout the text, as they are aimed at affording a deeper understanding and details, bringing complementary, but accessory information, which nevertheless enriches and illustrates the main text. Another objective is disambiguation, especially for molecules with multiple names and aliases. In the present text, footnotes are not intended to authorize a break, where what is not handled is hidden, although the knowledge of the process of interest often remains limited.

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Paris, France Marc Thiriet

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