Modeling and Simulation in Science,
Engineering and Technology

Giovanna Guidoboni
Alon Harris
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Editors

Ocular Fluid Dynamics

Anatomy, Physiology, Imaging Techniques, and Mathematical Modeling

Birkhäuser

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Preface

The book aims at providing an overview of the current theoretical approaches available to model ocular fluid-dynamics in health and disease, along with the outstanding questions in the related theoretical and clinical fields. The theoretical modeling of ocular biophysics is a fast-growing research field that is attracting more and more scientists from various disciplines. This book will serve as a comprehensive reference for current and future scientists interested in this field, who will find a broad picture of the state-of-the-art with respect to:

- main open questions, controversial issues, and conjectures related to fluid flow in ophthalmology that pose major challenges for future advances in clinical research
- experimental and clinical technologies available to visualize and measure various physical quantities related to ocular fluids
- mathematical and computational models that investigate various aspects of fluid flow in the eye

This book stems from the idea that new answers to outstanding questions may only come from the true interaction among scientists with different expertise, including mathematics, engineering, physics, computer science, biology, chemistry, physiology, ophthalmology, optometry, clinical science, and pharmacology. Since each scientist looks at the same question from a different angle and describes the question using a different language, this book aims at creating a hub where such different perspectives can be explored with open minds and collaborative spirits, thereby providing a genuinely interdisciplinary overview of this diverse research field that will help guide new scientific investigations and spark new ideas.

This book focuses on five fluids, specifically blood, aqueous humor, vitreous humor, tear film, and cerebrospinal fluid. Each fluid is examined individually in a different part of the book, each part sharing the same structure based on four sections summarizing:

- elements of anatomy and physiology pertaining to that fluid
- pathological consequences of alterations in that fluid

- imaging technologies currently available to measure and visualize information pertaining to that fluid
- modeling approaches currently available to study the flow of that fluid in the eye

The book concludes with contributed chapters on future perspectives in the fields of imaging and modeling with application to ophthalmology.

The book integrates contributions by experts who strived to utilize a language accessible to scientists across disciplines, without compromising the accuracy of the presentation. Importantly, the authors of the chapters in this book were the first to read each other's contributions, thereby giving this book the flavor of a monograph rather than a mere collection of independent papers.

We believe that this book will foster an interdisciplinary approach to the study of the eye that combines clinical and experimental methods, data-driven modeling (e.g., based on statistics and machine learning), and physically based modeling (e.g., based on physics and biochemistry). Each of these approaches has advantages and limitations. *Experimental and clinical methods* provide invaluable data and information on living systems, but it is very challenging to isolate and control all the factors that influence the function of the system in vivo. *Data-driven models* allow the identification of patterns and correlations within large datasets, but it is very challenging to elucidate the cause-and-effect mechanisms that give rise to such patterns and correlations. *Physically based models* provide virtual laboratories, where the mechanistic contribution of specific factors on cardiovascular and lymphatic physiology can be investigated theoretically, but it is very challenging to account for all possible factors and their natural variability among individuals. In addition, the relevance of theoretical predictions based on mathematical models is tightly dependent on the quality of the data that was used to calibrate model parameters and run the model simulations.

We hope that this book will serve as a catalyst for the integration of these three approaches in a novel paradigm to address disease prevention, diagnosis, and treatment in a precise and individualized manner, which represents the twenty-first century view of ophthalmology, and, more generally, of medicine.

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Part I
Introduction

Mathematical and Physical Modeling Principles of Complex Biological Systems

Riccardo Sacco, Giovanna Guidoboni, and Aurelio Giancarlo Mauri

Abstract A model of a complex system is a facsimile that can be used to investigate the problem at hand by simulating its behavior under specific conditions. Many modeling approaches are used in the applied sciences, including physical, animal, conceptual, and mathematical models. Specific examples will be provided in the chapter to illustrate the synergistic application of modeling to the simulation of biological fluid flow with relevance to ophthalmology.

1 Introduction

Problem complexity in Life Sciences and Engineering is becoming so prohibitive that the classic trial-and-error technique customarily adopted for investigation, design, and parametric optimization of a given system is no longer practicable and effective. Let us make this important concept more concrete by means of two specific examples, namely the pathology of open-angle glaucoma (OAG) and the production of memory devices for data storage.

OAG is a neuropathology of the optic nerve head that, by the end of 2020, will be the cause of blindness for almost 80 million individuals worldwide [28]. OAG is a multifactorial disease in which alterations of intraocular pressure, hemodynamic conditions, and metabolic functions, in conjunction with aging and epigenetic effects, concur in a nontrivial manner to determine the very often asymptomatic occurrence of the pathology and its progression. These multiple pathogenic factors make the search of the causes of OAG a very complex task and prevent the clinical scientist from the possibility of easily disentangling one specific factor from the

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others and quantify its relative impact on the onset of the disease in each individual patient.

Memory devices represent the most advanced level of Information and Communication Technology (ICT) ever since the continuous increase of electronic storage capabilities has initiated the so-called era of cloud computing [1]. The ICT boom is however close to a stop because the shrinking of device dimensions, main responsible of improvement of electronic component performance, has almost reached its ultimate limit predicted by Moore's law [22]. Such a negative perspective is prompting scientists and device designers to search for new technological solutions based on the joint adoption of new architectures and new materials. This challenge is still far from a conclusive answer.

The two above-described examples are striking paradigms of modern problems that must be faced nowadays in Life Sciences and Technology. As it is often the case, difficult questions call for sophisticated answers, thereby requiring the synergistic contribution of different competences and skills spanning from Mathematics to Physics and Engineering. Modeling can play a fundamental role by facilitating the integration of such multidisciplinary contributions to advance the understanding of complex systems.

2 A Broad View of Modeling: Meaning, Aims, and Approaches

Modeling means, in a broad sense, to create a sort of facsimile, henceforth referred to as the model, that can be used to study the main features of the system at hand and its behavior under specific conditions. Different approaches are used for investigation in Biology and Applied Sciences, including physical, animal, conceptual, and mathematical models. In the remainder of the chapter we provide a description of each of these modeling methods with specific examples in bioengineering.

2.1 Physical Models

Physical models are physical replicas of the system under consideration. Physical models are utilized extensively in engineering, biochemistry, and architecture to visualize important features of the design of an automobile, of the DNA structure, or of a civil structure. With the rapid development of three-dimensional printing, physical models provide medicine with powerful tools that facilitate education and surgical planning, with many potential benefits for training, research, and clinical interventions in ophthalmology [13]. Physical models may also be utilized in biomedical applications to reproduce some of the main features of a living

system and study them in a controlled experimental environment. For example, in [7, 8] a mock circulatory flow loop is utilized to investigate the flow conditions in the human abdominal aorta. Another example can be found in [20], where an ultrasound imaging chamber incorporated in a cardiac flow loop allowed two- and three-dimensional Doppler characterizations of both simple and complex models of valvular regurgitation.

2.2 Animal Models

Animal models consist of replicating in an animal a disease or an injury similar to a human condition. Animal species utilized for biomedical research include mice, dogs, pigs, and monkeys, whereas conditions of interest may be inbred, induced, or already existing in the animals. Animal models are very often the key to groundbreaking discoveries in Medicine and Life Sciences. For example, the research conducted on dogs by Frederick Banting showed that the isolates of pancreatic secretion were successful in treating diabetes. This led to the discovery of insulin in 1922, jointly with John Macleod and Charles Best [32]. Another example is the study on rhesus monkeys conducted by Jonas Salk in the 1940s, which led to the isolation of the polio virus and the creation of a polio vaccine [4]. In ophthalmology, animal models are utilized for the investigation of many pathological conditions, including glaucoma [5, 30], myopia [9, 24], and age-related macular degeneration [25, 29].

2.3 Conceptual Models

Conceptual models provide a scheme of cause-effect relationships that govern the behavior of a complex system. In biology, chemistry, and life sciences, conceptual models are typically used to represent the chains of reactions and mechanisms regulating specific functions. The advantage of conceptual models is that visualization of cause-effect relationships helps interpret the complex interactions existing among them. The limitation of conceptual models is that they are not quantitative and, consequently, they cannot predict how much and to what extent the system behavior will be affected by alterations in specific mechanisms.

2.4 Mathematical Models

Mathematical models are constituted by sets of mathematical equations and formulas whose solutions describe the behavior of a complex system or the probability that a specific event occurs. Thus, mathematical models can help translate conceptual

models into a solvable problem, whose solution may provide a quantitative tool to study the behavior of a complex system. Mathematical models can be classified into two main categories, namely data-driven models and mechanism-driven models, as described below.

2.4.1 Data-Driven Models and Statistical Viewpoint

Data-driven models aim at identifying patterns and trends within a given dataset by employing techniques based on statistical methods. Data-driven models typically consider very large datasets, which include data acquired by means of physical models, animal models, and studies on human subjects. The main outcome of a data-driven model is a set of correlations among relevant factors within the dataset. Despite recent progress to infer causality beyond correlations [16, 31], it is still very difficult to get information on the fundamental cause-effect relationships among physical and biophysical mechanisms that ultimately determine system behavior. An example of data-driven modeling applied to the study of glaucoma progression can be found in chapter "Statistical Methods in Medicine: Application to the Study of Glaucoma Progression".

2.4.2 Mechanism-Driven Models and Biophysical Viewpoint

Mechanism-driven models aim at providing quantitative information on the mechanisms that give rise to a given set of data. Mechanism-driven models are the mathematical translation of physical and biophysical principles, such as Newton's laws of dynamics, conservation of mass, electric charge, momentum, and energy. Mechanism-driven models are deterministic in nature, but can also include stochastic effects, and may be constituted by very different mathematical structures, such as algebraic relationships, ordinary differential equations, partial differential equations, and stochastic differential equations. This book provides a review of the mechanism-driven models currently available to investigate the flow of various fluids in the eye, specifically blood (see Chapter "Mathematical Modeling of Blood Flow in the Eye"), aqueous humor (see Chapter "Mathematical Models of Aqueous Production, Flow and Drainage"), vitreous humor (see Chapter "Mathematical Models of Vitreous Humour Dynamics and Retinal Detachment"), tear film (see Chapter "Mathematical Models of the Tear Film") and cerebrospinal fluid (see Chapter "Mathematical Modeling of the Cerebrospinal Fluid Flow and Its Interactions").

2.4.3 Synergy Between Statistical and Biophysical Viewpoints

Statistical and biophysical viewpoints are not in competition, rather, they are complementary and synergistic in the quest for a deeper understanding of complex systems. On the one hand, biophysical relationships identified via mechanism-driven models can be used to "inform" the statistical analysis about the existence of linear and/or nonlinear dependencies among covariates, which should be properly taken into account by the statistical analysis to avoid incorrect interpretations of trends in the data. On the other hand, stochastic variations of model parameters can be included in the biophysical models to account for individual variabilities and/or uncertainties in the measurements, whose influence on the biophysical outcomes can be quantified via statistical methods within data-driven models.

Ultimately, the synergy between statistical and biophysical models leads to a theoretical version of the complex system under investigation, which may serve as a *virtual laboratory* to perform theoretical experiments at low cost and in a short time, without the need of expensive equipment and resources. For example, a virtual laboratory could be used to:

- *simulate* several alternative scenarios to produce a quantitative prediction of system behavior, thereby allowing scientists to test and compare conjectures, as well as to formulate new ones;
- *compare* outcomes of existing studies (e.g. measurements on human subjects or physical and animal models) with simulations, thereby allowing scientists to interpret real data based on conjectured physical and biophysical mechanisms;
- *identify* factors that have a major impact on the system behavior, thereby providing a guide to the design of new experimental and clinical studies;
- *explore* levels of detail that current experimental techniques cannot reach due to instrumental limitation, thereby allowing scientists to investigate microscopic variables that may significantly affect the macroscopic function of the system.

3 Towards the Development of a Virtual Laboratory

The development of a virtual laboratory in Life Sciences is a highly nontrivial process that calls for a multidisciplinary effort. Conceptually, this process consists of five main tasks:

1. *problem definition*, where the main open questions in the applied field are identified and a strategy to address them is outlined;
2. *multiphysics/multiscale analysis*, where the relevant biophysical processes are identified and their spatial and temporal scales are characterized;
3. *model selection*, where the modeling approach is selected on the basis of its suitability to address the questions of interest and a specific mathematical problem is formalized;

4. *model solution*, where analytical or numerical techniques are utilized to obtain exact or approximated solutions to the specific mathematical problem;
5. *model assessment*, where the solutions of the specific mathematical problem are validated against experimental and clinical data.

In the next sections, each task is described in detail with reference to specific cases of interest in ophthalmology.

3.1 Problem Definition

The most stimulating, yet challenging, task of developing a virtual laboratory consists in pinning down important questions of interest in the applied field and devising a realistic strategy to address them. Oftentimes, this task is the most time-consuming, since it requires a dynamic interaction among scientists with different expertise, who often see the same problem from different viewpoints and utilize different languages to express them. The path leading to the definition of specific problems to be addressed through the use of a virtual laboratory is made of many steps, where areas of interest are successively refined until a set of well-formulated questions is shaped.

Let us make this concept more specific by means of an example in glaucoma research. As mentioned in Sect. 1, glaucoma is a multifactorial disease for which the only approved therapies aim at lowering the intraocular pressure (IOP), even though overwhelming evidence shows that IOP is not the only factor contributing to the disease [18, 19]. Thus, one of the main questions troubling ophthalmologists all around the world is:

Question *Level 0*	Why lowering intraocular pressure (IOP) is not enough to stop glaucoma progression in all patients?

This question provides the starting point and the overall motivation of the scientific investigation and, therefore, we refer to it as *Level 0*. This Level 0 question, however, is still too broad to be addressed by means of biophysical models. A series of more specific questions or conjectures is then compiled, such as the one below:

Each of the Level 1 questions listed above is further elaborated into specific problems that can be studied by means of a virtual laboratory. For example, starting from question (1a), we can define the following specific problems:

Questions *Level 1*	(1a) Does the same IOP level have the same consequences on different individuals?
	(1b) Are there other pathogenic factors, in addition to the level of IOP, that make some patients progress more than others?
	(1c) Should glaucoma be understood as a family of diseases sharing similar symptoms despite being characterized by different pathogenic processes?
	(1d) . . .

Questions *Level 1a*	(1a.i) What is the effect of IOP level on ocular biomechanics, including the distribution of stresses and strains in the tissues?
	(1a.ii) What is the effect of IOP level on ocular hemodynamics, including the distribution of pressures and velocities in the blood vessels?
	(1a.iii) What is the effect of IOP level on ocular oxygenation, including the distribution of oxygen in the blood vessels and in the tissues?
	(1a.iv) What is the effect of IOP level on the functionality of vascular regulation in the eye?
	(1a.v) What is the effect of IOP level on the flow of aqueous humor?
	(1a.vi) . . .

Each of the Level 1a questions listed above can be the starting point for the development of a specific mechanism-driven model that, as discussed in the sections below, may require different mathematical and computational methods. However, when working on a model addressing a specific problem, for example (1.a.ii), it is important to keep in mind that we are working on a piece of a big mosaic representing the *big picture*. In other words, the specific problem, say (1.a.ii), is part of a bigger problem that ultimately aims at understanding why lowering IOP, per se, does not always prevent progression to blindness (see question at Level 0).

3.2 Multiphysics/Multiscale Analysis

Once identified a specific problem to address by means of a virtual laboratory, an interdisciplinary effort is required to identify the biophysical factors and processes that are likely to play a role in determining system behavior. Considering again the example of problem (1.a.ii), some of the most relevant factors and processes include (being not limited to):

- systemic factors driving blood flow, such as blood pressure and vascular regulation;

- mechanical properties of blood vessels, such as stiffness and compliance;
- biochemical processes at the cellular levels, such as nitric oxide absorption and myosin phosphorylation in the smooth muscle cells;
- intracellular chemical reactions, such as intracellular calcium uptake-release.

It is important to emphasize that, in the human body, all the factors and processes listed above take place simultaneously, even though at very different scales in space and time. Specifically, we can identify the following hierarchy of spatial scales:

- a *macroscale* (corresponding to the whole body) whose characteristic spatial length is of the order of meters;
- a *mesoscale* (corresponding to a specific organ) whose characteristic spatial length is of the order of centimeters;
- a *microscale* (corresponding to a single cell) whose characteristic spatial length is of the order of micrometers;
- a *nanoscale* (corresponding to the cellular membrane) whose characteristic spatial length is of the order of nanometers.

In addition, we can identify the following hierarchy of temporal scales:

- a *macroscale* (corresponding to a lifetime) whose characteristic temporal length is of the order of years;
- a *mesoscale* (corresponding to a day) whose characteristic temporal length is of the order of hours;
- a *microscale* (corresponding to the heartbeat) whose characteristic temporal length is of the order of seconds;
- a *nanoscale* (corresponding to the cellular reactions) whose characteristic temporal scale is of the order of microseconds (or even less).

Thus, spatial and temporal scales characterizing the biophysical processes within the human body span over 9 orders of magnitude. It is therefore no surprise that accounting for such an enormously wide spectrum of scales within a single mathematical model, despite theoretically possible, may be prohibitive and unaffordable even for the most powerful existing computational facilities. However, the link between the different scales is an essential part of life. For example, the onset and progression of glaucoma occurs over decades as the result of subtle damage to the ocular tissues occurring at every ion exchange within the heartbeat. Thus, the development of a sound mechanism-driven model in the context of life science should account for the multiscale and multiphysics nature of Life, while balancing between biophysical accuracy and model complexity. How to effectively and accurately attain this balance remains one of the biggest challenges in applied mathematics.

3.3 Model Selection

Mathematical models can be divided into two main categories: lumped parameter (LP) models and distributed parameter (DP) models. LP models mathematically represent the biophysical problem at hand by the construction of an equivalence with an electrical circuit. In this approach, the biophysical system is described by means of a network of interconnected electrical equivalent elements typically including resistors, capacitors, inductors, and current/voltage sources. The variables determined by a LP model are usually the nodal values of the electric potential and the branch currents in the network, which, in the electric analogy to fluid flow, correspond to the fluid pressure and the flow rate, respectively. DP models mathematically represent the biophysical problem at hand by means of a continuum-based geometrical description of the medium in which phenomena and processes take place. Phenomena are typically governed by fundamental laws of Physics and Mechanics such as mass, charge, and momentum conservation principles. Unlike LP models, the solution variables of a DP model are functions of position and time, rather than nodal values and/or branch currents. LP and DP models have both advantages and disadvantages. LP models provide a systemic view of the problem dynamics at low computational costs, but do not allow a detailed description of local spatially dependent phenomena. Conversely, DP models provide detailed spatial descriptions of the system under investigation, typically at the price of a much higher computational effort and allocation of memory resources. The decision of whether to adopt a DP or LP model is not trivial and depends on numerous factors, including the level of accuracy that is required to the model solution compared to the level of accuracy in the knowledge of model parameters and input data. In the following, we provide two examples for the applications of LP and DP models to the study of different aspects of ocular biophysics, namely the interplaying role of IOP, blood pressure and blood flow in the determination of retinal blood flow (see Sect. 3.3.1), and the interplaying role of electrochemical and fluid dynamical mechanisms in the production of aqueous humor by the ciliary processes (see Sect. 3.3.2).

3.3.1 Lumped Parameter Model of Blood Flow in the Retina

In this section we provide an example of the use of a lumped parameter model in ophthalmology, referring to [12] and chapter "Mathematical Modeling of Blood Flow in the Eye" for all the mathematical details, simulation results, and comments. The main goal of the investigation is to utilize a mechanism-driven approach to shed light on the complex interaction among risk factors in glaucoma. To this end, a LP mathematical model is developed to simulate blood flow through the central retinal artery (CRA), central retinal vein (CRV), and retinal microvasculature. In this approach, variable resistances are used to describe active and passive diameter changes due to vascular regulation and intraocular pressure (IOP). In the mechanistic description, blood flow is:

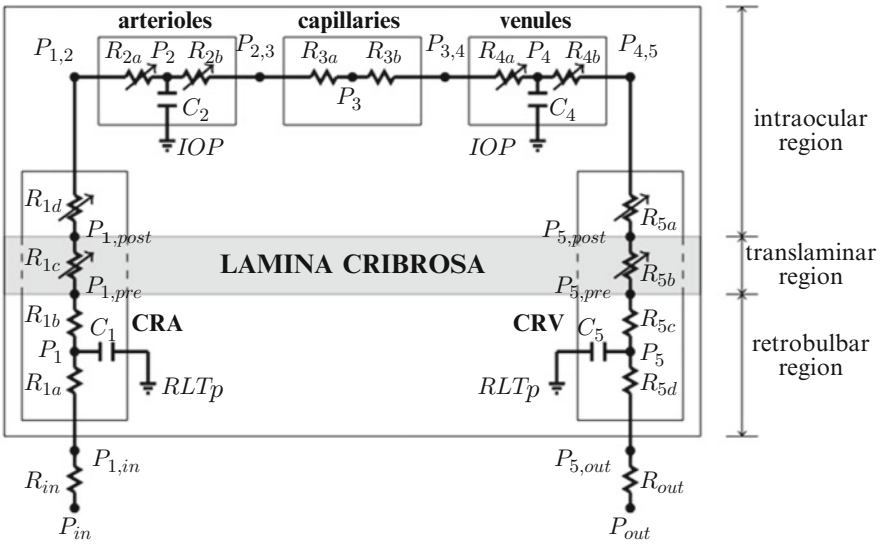

Fig. 1 Schematic representation of a mechanism-driven, lumped parameter model to study the relationship between IOP, blood pressure, and blood flow in the retina (figure reproduced from [12])

- driven by the difference between input and output pressures (denoted by P_{in} and P_{out}, respectively);
- impeded by the combined action of IOP and retrolaminar tissue pressure (RLTp);
- modulated by vascular regulation.

A schematic of the model is reported in Fig. 1. In the LP description of blood flow throughout the retinal microvasculature, the nodal pressures P_i are functions of the sole time variable in such a way that, at each time instant, their value biophysically represents the spatial average of blood pressure in the considered vascular compartment. For example, referring to the scheme of Fig. 1, the nodal pressure P_1 is the spatial average of the blood pressure in the CRA, P_2 in the arterioles, P_4 in the venules, and P_5 in the CRV. The mathematical formulation emanating from the electrical equivalent circuit of Fig. 1 consists of the solution of a system of nonlinearly coupled ordinary differential equations for the nodal pressures P_i, with $i = 1, 2, 4, 5$.

The proposed lumped parameter model is used to simulate retinal blood flow for three theoretical patients with high, normal, and low blood pressure. The model predicts that patients with high and normal blood pressure can regulate retinal blood flow as IOP varies between 15 and 23 mm Hg and between 23 and 29 mm Hg, respectively, whereas patients with low blood pressure do not adequately regulate blood flow if IOP is 15 mm Hg or higher. Thus, hemodynamic alterations are predicted to impact patients' health conditions only if IOP changes occur out of the regulating range, which, most importantly, depend on blood pressure.

These theoretical predictions have been recently confirmed by the population-based study conducted in [33] over nearly 10,000 individuals (nearly 20,000 eyes), in which it has been found that patients with the highest probability of the occurrence of glaucoma are those exhibiting a combination of low blood pressure and elevated IOP.

3.3.2 Distributed Parameter Model of Aqueous Humor Production in the Ciliary Process

In this section we provide an example of the use of a DP model in ophthalmology, referring to [21] for all the mathematical details, simulation results, and comments. The main goal of the investigation is to utilize a mechanism-driven approach to shed light on the role of bicarbonate ion on the active secretion of aqueous humor across the membrane of the nonpigmented epithelial cells of the ciliary process. To this end, a distributed parameter mathematical model is developed to simulate the coupled interaction between ion electrodynamics and aqueous humor flow into the basolateral space adjacent to the nonpigmented epithelial (NPE) cells. In the mechanistic description, ion electrodynamics is driven by the balance between:

- a gradient in ion concentration across the membrane;
- an electric field generated by the transepithelial potential difference across the membrane and by the ions in motion throughout the membrane;
- the translational velocity of the aqueous humor flowing across the membrane.

In the mechanistic description, active secretion of aqueous humor is driven by the balance between:

- a fluid pressure gradient across the membrane;
- a shear stress between fluid elements moving with different velocity;
- an electric pressure due to the ions flowing inside the aqueous humor fluid.

A mathematically simplified cylindrical three-dimensional geometry of the transmembrane channel that has been used in numerical simulations is reported in Fig. 2.

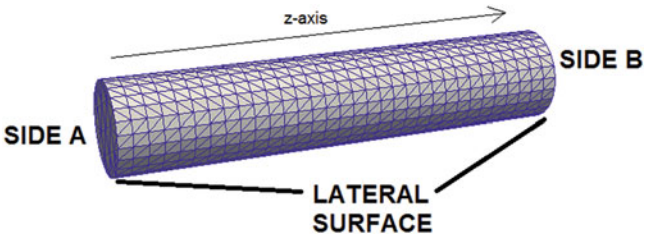

Fig. 2 Geometry of a NPE transmembrane channel. Side A represents the intracellular NPE region, Side B represents the extracellular region in the basolateral space. The thickness of the channel is 5 nm (figure reproduced from [21])

In the DP description, unlike the case of the LP description, the dependent variables of the problem are also functions of the spatial position, mathematically represented by a three-dimensional vector $\mathbf{x} = (x, y, z)$, where z is the cylinder axial coordinate, whereas x and y are the coordinates in the plane orthogonal to the z axis. Thus, the mathematical formulation consists of the solution of a system of nonlinearly coupled partial differential equations for the electric potential, the ion concentrations of bicarbonate, sodium, potassium, and chloride, the aqueous humor pressure and velocity, which depend both on temporal and spatial coordinates.

The proposed DP model is used to disentangle the contribution of bicarbonate from that of the other ions, which is very difficult to investigate experimentally, in the formation of the transmembrane epithelial potential difference V_m and in the secretion of aqueous humor into the basolateral space. Model predictions indicate that V_m is close to baseline experimental measurements only if bicarbonate is included in the simulation. Model simulations of the sodium-potassium (Na/K) pump indicate an efflux of sodium and an influx of potassium, in accordance with pump physiology. The simulated Na/K ratio is 1.53, which is in very good agreement with the theoretical stoichiometric ratio of 1.5. The above theoretical model predictions suggest that bicarbonate inhibition may prevent physiological baseline values of the nonpigmented transepithelial potential difference and Na/K ATPase function, thus providing useful indication in the design of medications to decrease active secretion of aqueous humor.

3.4 Model Solution

The two examples illustrated in Sect. 3.3 demonstrate that the use of LP and DP models for the simulation of complex biophysical problems leads to sophisticated systems of differential equations. Finding the exact solution of such equations is impossible unless drastic simplifications are introduced in the mathematical formulation, such as, for instance, in the electric equivalent circuit of Fig. 1, transforming the nonlinearly varying resistors into linear resistors. This approach has the advantage of making the analysis treatable at the price, however, of neglecting significant biophysical features of the system under investigation. In order to cope with the mathematical model in its more general integrity, it is therefore mandatory to resort to numerical approximation techniques. We refer to [2, 17] for the numerical treatment of ordinary differential equations and to [15, 27] for the numerical treatment of partial differential equations. In the following, we give a very short introduction to the concept of numerical approximation of a mathematical problem and to the notion of approximation error, which is the difference between the exact solution of the mathematical problem and the solution of its approximation. In addition, we shortly address the issue of the actual implementation of a numerical method into a computing machine environment, with special emphasis on the notion of finite arithmetics and machine precision.

3.4.1 The Mathematical Problem

Let us denote by D the space of admissible data and by $d \in D$ a given value of the data. Let also denote by V a vector space. Typically (but not necessarily) V has infinite dimension. The abstract formulation of a mathematical problem is:

Given $d \in D$, find $x \in V$ such that

$$F(x, d) = 0 \tag{1}$$

where F is the functional relation between x (the solution of (1)) and d (the input data of (1)). In general, it is not guaranteed that (1) admits a unique solution or that it is even solvable. In what follows we assume that (1) is *well-posed*, meaning that it admits a unique solution and that such solution depends with continuity on the data (see for further details [26, Chap. 2]).

3.4.2 The Numerical Problem

As previously anticipated, solving (1) exactly is, in general, very difficult or even impossible. Thus, we associate with problem (1) the following family of numerical problems:

Given $d_h \in D_h$, find $x_h \in V_h$ such that

$$F_h(x_h, d_h) = 0 \tag{2}$$

where D_h and V_h are finite dimensional subspaces of D and V, respectively, whereas d_h and x_h are the approximation of the input data d and of the exact solution x in D_h and V_h, respectively. The quantity h is a positive number usually referred to as discretization parameter. Referring to the examples illustrated in Sect. 3.3, we may think at h as the incremental time step and/or the spatial grid size. As in the case of problem (1), also (2) is assumed to be well-posed. The main, fundamental, difference between (1) and (2) is that x_h is sought for in a finite-dimensional space so that the solution of (2) is computable whereas the solution of (1) is, in general, not.

3.4.3 Approximation Error and Convergence

In general, x_h and x obviously do not coincide. Therefore, we define the *approximation error* intrinsically associated with (1) and (2) as

$$e_h := x - x_h \,. \tag{3}$$

The requirement for (2) to be a good approximation of (1) is the *convergence* of x_h to x, which is mathematically stated by the following limit

$$\lim_{h \to 0} e_h = 0 \,. \tag{4}$$

Thus, as intuitively understandable, we expect x_h to get increasingly close to x as the discretization parameter becomes increasingly fine. At the same time, we also expect d_h to converge to d as h becomes small, so that, should x_h converge to x, the following property is satisfied

$$\lim_{h \to 0} F_h(x_h, d_h) = F(x, d) \,. \tag{5}$$

This latter relation means that the approximate and the exact problem tend to coincide when we have convergence of *both* data and solution.

3.4.4 Computer Implementation

Even if the solution of the numerical problem (2) is computationally affordable, this does not necessarily mean that it is also computationally easy to achieve. In other words, we need in general to *implement the actual computation of* x_h *within an algorithm* that is then to be run on a computer machine. In the hardware, any real number y is replaced by a *machine representation* called floating-point number and denoted by $fl(y)$. It is important to emphasize that $fl(y)$ is *NOT*, in general, equal to y; rather, there is an intrinsic error that adds to the discretization error introduced in (3). This additional source of error is called *round-off error*, and can be estimated as follows

$$fl(y) = y(1 + \delta) \tag{6}$$

where δ is small quantity of the order of 10^{-16}. From (6) we see that any input datum in a computer machine may, in general, be affected by a "native" error. This error is a very small quantity and is the result of the *finite precision* of the computer hardware in storing any number in the memory. This is the reason why δ is also referred to as *machine precision unit*. The fact that the machine precision unit is a very small quantity is, of course, good news. However, it is very important to keep in mind that the effect introduced by machine precision on numerical computations may not always be negligible, as it happens, for example, to the error due to numerical cancellation of significant digits that is introduced by the finite arithmetic of the computer (see [26, Sect. 2.4]).

3.4.5 The Issue of Stability

The principal objective in the design of a numerical problem is to ensure the convergence of x_h to x, as stated by relation (4). It can be shown (see [26, Sect. 2.2.1]) that a necessary condition for (4) to hold is that the numerical problem (2) is *stable*.

Stability is strictly related to the mathematical notion of *continuous dependence on data*. To better explain this latter concept, let us consider a perturbation δd_h in the data d_h such that the modified data is $\widetilde{d}_h = d_h + \delta d_h$ and assume that $\widetilde{d}_h \in D_h$ as it was for the unperturbed data d_h. Correspondingly, consider the *perturbed numerical problem:*

Given $\widetilde{d}_h \in D_h$, *find* $\widetilde{x}_h = (x_h + \delta x_h) \in V_h$ *such that*

$$F_h(\widetilde{x}_h, \widetilde{d}_h) = 0. \tag{7}$$

The numerical model enjoys the property of continuous dependence on data (equivalently, it is stable), if the perturbation in the solution δx_h is small when the perturbation in the data δd_h is small too. To quantify this concept, we associate with the numerical problem (2) the *condition number* $K \geq 1$. This number provides an estimate of the amplification that may be introduced to δd_h by problem (2). If K is not much larger than 1, then the perturbation δx_h will be not much larger than δd_h, so that we can conclude that problem (2) is *well-conditioned* and the computed solution x_h is reliable. Conversely, if $K \gg 1$, then the perturbation δx_h may be much larger than δd_h, so that we can conclude that problem (2) is *ill-conditioned* and needs to be handled with particular care in order to obtain a reliable numerical approximation. Oftentimes, ill-conditioning is addressed by means of a suitable stabilization of (2). Examples of this latter method are represented by the regularization techniques that allow to transform an ill-conditioned problem into a well-conditioned problem (see [23]) or the stabilized finite element formulations for the numerical approximations of partial differential equations proposed in [6, 10, 14].

3.5 Model Assessment

It is extremely important to keep in mind that the numerical solution of a mathematical model does not conclude the process of model development. As a matter of fact, once the problem has been defined and the corresponding mathematical model has been solved, as discussed in Sects. 3.4.1–3.4.4, we obtain as a result some predictions of the behavior of the investigated system. These predicted results must be compared with experimental data that can assess the validity of the assumptions that were made to derive the model in the first place. Depending on whether or not the model results are capable of capturing the essential features of the biophysical system, it may become necessary to revisit the whole definition of the mathematical problem and to modify certain assumptions that proved to be overly simplistic.

An example of the importance of model assessment is provided in Sect. 2.1.2 of chapter "Mathematical Modeling of Blood Flow in the Eye", where the mathemat-

ical modeling of venous collapsibility in the retina is discussed. When modeling venules as compliant tubes, thereby adopting the renown Laplace law, the model depicted in Fig. 1 predicts that retinal venules do not collapse even in the case when IOP is higher than their intraluminal pressure. This model prediction is clearly in contrast with the experimental observations on cats reported by Glucksberg and Dunn [11] and Attariwala et al. [3], where open retinal venules, i.e., not collapsed, were seen only for IOP values lower than their intraluminal pressure. This inconsistency between model predictions and experimental observations demanded a reassessment of the model assumptions. In particular, by representing the venules as collapsible tubes, thereby substituting the Laplace law with the law for collapsible tubes (Starling resistors), the model predictions demonstrated to be consistent with the experimental findings. A comparison between the intraluminal pressures computed when adopting the Laplace law and the law for collapsible tubes is reported in Fig. 13 of chapter "Mathematical Modeling of Blood Flow in the Eye".

We would like to emphasize that this example also illustrates the importance of gathering reliable experimental data, which, in addition, should be correctly interpreted and utilized when developing the mathematical model. Thus, the construction of a mathematical model for the study of a biophysical system is a truly interdisciplinary endeavor that calls for team work across disciplines and competencies.

4 Conclusions and Perspectives

Problem complexity requires new tools for achieving a satisfactory solution and producing significant advances in knowledge and technology. In this perspective, the adoption of mathematical modeling can be a valuable approach, especially when it is based on physical principles and calibrated against a set of real data. In this chapter, we provided a short introduction to the paradigm of modeling and to the rationale that leads from the phase of *problem definition* to the phase of *model assessment*. Specific examples have been included to illustrate the use of mathematical modeling in the study of different aspects of ocular biophysics, namely the interplaying role of IOP, blood pressure and blood flow in the determination of retinal blood flow, and the interplaying role of electrochemical and fluid dynamical mechanisms in the production of aqueous humor by the ciliary processes.

The fascinating conclusion that can be drawn from the content of this chapter is that mathematical modeling is a very general and powerful technique to address the solution of a complex problem in Engineering and Biology. A particular feature, which makes it unique and versatile, is the ability to develop an *abstract picture* (the model), which relates the specific problem (for example, the blood flow in the retina) to a general framework by means of connections and analogies (for example, the electric analogy to fluid flow depicted in the circuit of Fig. 1). The benefits of drawing this abstract picture are twofold. On the one hand, the model user can take advantage of existing algorithms, possibly developed for other types

of applications and yet sharing the same structure. On the other hand, the model developers may discover new theoretical and computational challenges that call for new methodologies to be devised. Thus, the development and utilization of mathematical models as virtual laboratories is a genuine interdisciplinary endeavor that has significant impacts across disciplines, from engineering to medicine.

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Part II
Blood

Vascular Anatomy and Physiology of the Eye

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Abstract This chapter provides an overview of the main structural and functional properties of the ocular vasculature. Four major circulatory systems within the eye are considered, namely those nourishing the retina, the optic nerve head, the choroid, and the anterior segment. Some aspects related to vascular regulation and innervation are also discussed, along with outstanding questions that remain a matter of debate.

1 Introduction

Blood circulation in the eye is structured in a very complex way in order to nourish the tissues without interfering with visual function. Interestingly, some components are extremely rich in blood, such as the choroid, whereas others are completely avascular, such as the vitreous humor, lens, and central regions of the cornea and fovea. Some of the most relevant ocular components are schematized in Fig. 1.

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