Preface

Mathematical modeling

The modeling of a complex system can be decomposed into three phases. Phase I consists in identifying its functions (most organs in the human body have more than one), to introduce quantities that are relevant with respect to those functions, and to design relations (equations) between those quantities in order to obtain a mathematical problem. Among those quantities some are called *unknowns*, or variables, and some are *data* (their values are supposed to be known). Note that there might be different levels of models for the same phenomena, and that a quantity may happen to be an unknown in some model, and a data in another one. Once a mathematical *model* is obtained (see below some remarks on this very phase of elaboration), its suitability from a mathematical standpoint can be investigated, or analyzed (phase II): does it admit a solution, is this solution unique and stable with respect to perturbations of the data[1]? Once this *well-posedness* has been established[2], the model has to be confronted with the reality that it is intended to reproduce in some way (phase III). This delicate phase of the modeling process can be mathematical in nature, e.g. by proving that the solution can be shown rigorously to behave in some manner that is consistent with observations. Validation of the model can be complemented by direct comparisons of experimental measurements with analytical or computed solution to the mathematical model. This confrontation phase can be extremely difficult because it usually amounts to answering two questions at the same time:

- is the model valid?
- assuming that the model is valid, which set of data best corresponds to reality?

It is in particular well known that a “rich” model (with many parameters) confronted to a “poor” reality (experimental data are parcimonious) is likely to answer successfully the second question, in the sense that one will be able to find a set of parameters

[1] This feature is essential for the model to be considered as relevant, since, especially in the domain of life sciences, the data are usually not known exactly, and may vary from one individual to the other. It is known as Stability in the sense of Hadamard.

[2] This well-posedness provides satisfaction to the mathematician, but it does not usually say anything on the adequacy of the model with the underlying phenomenon. It just provides a sound framework for the third phase.

which allows to reproduce the experimental data, even if the model itself does not contain the important features of the underlying phenomena.

The overall process is not mathematical as a whole, although it may involve sophisticated mathematical tools (in phase II, or in phase III, to compute approximations of the exact solution in an appropriate way, or to identify parameters). The first phase is the core of the modeling process, as it conditions the content of the other two. The term *modeling* quite commonly refers to this very phase of elaboration of the mathematical equations.

Two main types of strategies can be followed to elaborate mathematical models, which are commonly referred to as Bottom Up (BU) and Top Down (TD) strategies. The BU approach consists in starting from the finest level at which the reality can be described by basic, unquestionable laws (like Newton's law for mechanical systems). In the context of lung modeling it could consist in writing equations at the level of alveoli, or capillaries if one is interested in perfusion. This is likely to lead to a huge number of unknowns, to call for knowledge of several parameters, etc. … Modeling in this context consists in performing some type of *homogenization* process, i.e. in attempting to replace those multiple unknowns and complex data by average quantities, or at least quantities defined at a coarser level of description. On the other hand, the Top Down approach consists in directly introducing global quantities, even if their link with actual quantities at the microscopic level does not make a clear sense at first, and try to identify some functional relations between those quantities, keeping as respectful as possible of the underlying expected phenomena. The approach then consists in confronting the model with reality, and in trying to enrich it. Considering the 3-phase approach that we presented, it consists in performing phase I, trying to find the simplest model (i.e. with the least unknowns, with the simplest equations), then performing phases II and III, and then starting again from I by adding some sophistication to the first model if necessary, and so on. This approach is usually based on representations of simplified versions of the reality (which are also called *models*, although this is not in the sense of the mathematical model we presented previously).

As an example, air flow through the lung is driven by negative pressures at the 300 million alveoli. The Top Down approach (which is detailed in Chapter 2) consists in mentally replacing those alveoli by a single balloon, in which the pressure is uniform. Note that such a model could be elaborated in a BU approach, by making some assumptions on the regularity of the geometry, on the uniformity of the collection of 300 million values, etc. … But the balloon model makes sense *per se*, and was actually introduced at a time where most data on the microscopic structure of the lung were not yet available. Note that TD approach is commonly based on quantities that are accessible to measurements, which makes comparison with experiments straightforward.

In the actual modeling process a mixture of both TD and BU strategies is usually followed. In the present book, the overall process is of the TD type[3], but the steps

[3] It presents the advantage to lead to a progressive increase in terms of complexity, which makes the beginning of this book accessible to undergraduate students.

of enrichment of the model present some BU characteristics: addition of a feature to obtain the next level model is usually based on a description of the reality at a finer scale.

We would like to end this general introduction on the modeling process by pointing out cultural differences between scientific communities. It is common in most applied sciences to talk about *numerical modeling*, which denotes the process of building a numerical procedure to compute quantities that aim at reproducing some real process. The relevance of the approach is then asserted by comparison with experiments or more generally unquestionable information which is available on the real process. Mathematics impose a different standpoint, which strictly separates the modeling process and the numerical approach. The present book is based on the latter philosophy, which consists in elaborating equations, we shall say *continuous* equations [4] (time, and space whenever it is relevant, are considered as continuous parameters). These equations can be studied as mathematical objects, it can be of great interest for example to establish some properties of the solutions which are known to hold true for the real observable quantities. As no analytic solution[5] exists in general, quantitative knowledge of these solutions calls for numerical discretization, i.e. reduction of the unknowns to a finite number, accessible to computer simulation, in a way that the computed solution can be expected to approximate the exact one. It raises of course a fundamental issue, which pertains to the correctness of the approximation process. The questions raised by this process are of mathematical nature, and it is a research domain *per se*, called *Numerical Analysis*. The typical contribution of Numerical Analysis consists in providing a fully rigorous result asserting that, as the discretization parameter goes to zero (e.g. the time step used in Ordinary Differential Equations), the computed solution *converges* to the exact one[6]. This approach may seem more rigorous than the integrated one (which does not give rise to mathematical treatment), and we advocate for it in the present book. Yet, we must insist on the fact that performing a full and rigorous numerical analysis does not provide any information on the model in terms of relevance and adequacy to reality, it simply enables to trust the discretization process, and thereby to consider the computed solution as reflecting the behavior of the continuous equations, without bias.

Mathematical modeling in life sciences

Most phenomena described in this book are of standard physical nature, in the sense that they follow well-known physical principles, mainly borrowed from Classical Mechanics. This raises the question: can the respiratory system be considered and described as an industrial process would be? More generally, in the context of mechanical modeling, is there a reason to make a strict distinction between living

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[4] These are called Ordinary Differential Equations (ODE) when it consists in following a finite number of quantities over the time, and Partial Differential Equations (PDE) when more than one variable is present, typically the time plus one or more space variables.

[5] It roughly means that there is no way to explicitly write the solutions by means of standard, well-known functions.

[6] It means that it can be made arbitrarily close to the exact solution.

organisms or inert material? As we shall see, a great amount of the tools developed in the context of industrial processes (like hydraulic pumps) are directly applicable to some parts of the ventilation process. Yet, modeling in life sciences presents some particular features that makes the modeling approach obey different rules, and even calls for new mathematical or numerical developments. We would like to describe here some of these particular features:

1. The microscopic reality is so complex that a direct Bottom Up approach, to use the terminology which we introduced previously, is out of the question. Most body tissues are irrigated by blood vessel of different sizes and shapes, large molecules like proteins (e.g. *collagen* or *elastin*) are likely to influence the mechanical behavior, and the matter itself is in constant change or renewal. It calls in most cases for a Top Down approach: macroscopic parameters are measured and their definition itself relies on models which are inferred by the experiment on observable effects, and not deduced from a sound microscopic basis.
2. All parameters that can be defined in the modeling process are highly variable. Even for a given subject, relevant parameters may vary in time. Experimental measurements give values with uncertainty, and different measurement protocols are likely to yield different values. All those sources of uncertainty or variability necessitate to pay a special attention to the effect of variations of the parameters upon the model outcomes.
3. Different phenomena are entangled, so that it is hardly possible to model single processes separately. As a direct modeling of the global system (the living organism as a whole) is usually out of reach, it calls for introducing multi-compartment models, with different levels of descriptions to achieve tractability of the obtained system, while keeping track of the most significant interactions between compartments.
4. Many biological processes, such as the ventilation process, can be seen as periodically forced dynamical systems. In the context of Ordinary Differential Equations or Partial Differential Equations, mathematicians have given a central place to the so called *Cauchy problem*, or *initial value problem*, which consists in describing the system at an instant considered as initial, and wonder whether a solution to the problem can be defined starting from the prescribed state, study its long time behavior, etc. … The problem here is different: the *initial value problem* does not make much sense: more relevant are questions regarding to *periodic* solutions: do they exist, are they unique, are they stable with respect to the data?

Blood and air networks

A huge and multidisciplinary literature (physiology, physics, mathematics, computer science) has been dedicated to the modeling of the blood network, from the heart to the smaller vessels, and this domain provides some tools to handle the respiratory system. The respiratory and vascular systems raise indeed some common issues in terms of modeling. First of all, the complexity of both networks calls for a decomposition into subsystems, and the coupling between those subsystems (e.g.

coupling between Navier-Stokes and Poiseuille's models for the lung, fluid-structure interaction problem coupled with a one-dimensional Shallow Water-like equation in the vascular context), presents some common features. Yet, both problems have their own characteristics: the density of the blood is similar to that of the surrounding medium, which leads to strongly coupled fluid structure interaction problems, whereas the mechanical coupling between the solid part of the lung and the air is essentially one-way because of the relative lightness of air. Besides, the blood transport system relies on a closed loop network (some substances can be exchanged with the outside world, like oxygen of carbon dioxide, but the fluid system is closed), whereas the respiratory system is, in essence, open.

Context, scope of the book

The modeling of respiration is still a domain of active research, and many aspects remain controversial, or at least not fully understood. Let us give a few examples of unresolved issues:

1. When a parameter is introduced in the context of lung modeling, a difference is usually made between the *morphometric* approach and the *physiological* one. The morphometric approach consists in using direct measurement of geometrical data and physical parameters to estimate the value of a quantity. From the physiological standpoint, the quantity is defined through a model, the output of which is accessible to direct measurement, and the value is determined by fitting the model output to the actual measurement. As an example, the capillary volume V_c is the volume of blood available, at some instant, for gas exchange. It can be seen as the volume of blood contained in the capillaries in the neighborhood of the alveoli, and its value can be estimated from the morphometric data pertaining to capillary number, capillary dimensions, number of alveoli, etc. … On the other hand, from a physiological standpoint, this volume quantifies the amount of oxygen which can be uptaken by blood. Both standpoints may lead to different values, and thereby induce questions about the very definition of the capillary volume. For example, the fact that the morphometric value is larger than the physiological one may lead us to consider that some part of the volume, in the morphometric sense, is actually not available for gas exchanges, due to defects in the ventilation, or impairing of the alveolo-capillary membrane. This issue is present at all stages of the modeling process, and a discrepancy between the two approaches generally suggests that some aspects of the considered phenomenon have not been properly accounted for in the model. According to the classification that we introduced previously, the morphometric standpoint corresponds to a *bottom-up* approach, whereas the physiological one, which focuses on global quantities, is of the *top-down* type.
2. To instantiate the previous general considerations, let us mention the question of *diffusing capacity* (also called transfer factor) of the respiratory system. This quantity is defined using a relation between the transfer rate of oxygen (or any other substance like carbon monoxide) and the difference between oxygen partial pressures in the alveolar air and in the blood. For more than sixty years, this dif-

fusion capacity has been considered as the sum of two contributions. The first one pertains to the membrane itself, and its definition follows Fick's law of passive diffusion; the second one accounts for the complex interactions between oxygen and hemoglobin, together with possible kinetic limitation effects. The latter is not directly accessible to measurement, it cannot be estimated according to a morphometric approach, and its physiological interpretation is not fully understood. Yet most quantities pertaining to the modeling of the transfer process (such as the capillary volume that we mentioned previously) are defined and estimated within this framework.

3. In the context of spirometry, the patient is required to perform a deep inspiration, followed by a maximally forced expiration. Volumes and fluxes are measured dynamically during the maneuver, and the corresponding plot (flux rate vs. volume) is used by the pneumologist to identify diseases that may affect the patient (like asthma, emphysema, fibrosis …). The pressures involved in the expiration phase are much larger than those in the case of a ventilation at rest, and the compliance of the respiratory tract (the fact that it may deform under external forcing) is known to play a determinant role, in particular in the first instants of the forced expiration phase. The manner a strong external pressure is likely to decrease the diameter of branches, thereby inducing an increase of the resistance which tends to limit the peak flow, cannot be fully described, in a quantitative way, by the existing mechanical models.
4. The role of the smooth muscle, which tends to decrease the diameters of the branches, is controversial. Its importance as a selective advantage is questioned in the medical literature, as it may harm the ventilation process e.g. in patients with asthmatic conditions, while its positive influence for healthy subjects is not clearly proven.

It would be highly presumptuous to claim that this monograph gives a definite response to all issues pertaining to this research area, and in particular to the points which we made above. We rather propose here a collection of theoretical and numerical tools to address the different aspects of this complex process. This book is also meant as an introduction to mathematical modeling, in the particular context of the respiratory system. We describe in details the process of building equations out of an observable reality together with measurable phenomena, and we investigate how the mathematical properties of those equations shed a light on the phenomenon that they aim at describing. We have tried to be as true to reality as possible, and we hope that some of the approaches presented here will serve in the future to improve knowledge of this fascinating organ, but we must confess that the pleasure to create models and to play with them may have driven us, in some occasions, quite far away from the clinical and experimental realities.

We must add that, at the end of the reading of this book, the reader will probably join the author in being left with much more questions than answers.

Intended audience

Most chapters of this book start with quite elementary considerations that only require a elementary knowledge of basic mathematics, in particular in differential calculus. A little experience in numerics may help to follow some sections dealing with those aspects. As for physiology, no prior knowledge is expected, but non specialist readers are strongly encouraged to carefully read Chapter 1. It gives a description of the respiratory system and some elements on the modeling approach. As a consequence, most of the book is accessible to motivated undergraduate students, with the exception of Chapters 4 and 6, which rely on infinite dimensional spaces (functional spaces to formulate Partial Differential Equations in Chapter 4, infinite networks for Chapter 6). Chapter 5 also contains some developments based on PDE's.

Exercises are proposed in all chapters to help the reader familiarize with the various concepts and techniques. Solutions are collected in Appendix A. Appendix B contains some basics (Ordinary Differential Equations, Partial Differential Equations, and Finite Element Method) that are mostly used in Chapters 2 and 4. To illustrate some of the numerical approaches that are described, some additional files (mainly Matlab and Freefem++ code files) are proposed to the reader. They can be downloaded from the Springer Extra Material platform (http://extras.springer.com).

All chapters are intended to be self-contained, with the exception of discussions on the existing literature and potential extensions of the presented material, which have been put at the end of chapters.

Outline of the book

Chapter 1 gives a general presentation of the respiratory system, orders of magnitude, most relevant mechanisms, and gives some ingredients for lung modeling.

The book goes on, in a more formal way, with different approaches which can be taken in an increasing order in terms of complexity. At the bottom of this hierarchy, we have the so-called lumped models, based on a small number of parameters (Chapter 2). As for mechanical aspects the simplest model relies on the sole volume of air contained in the lungs, and takes the form of a dissipative spring-mass system with dissipation. This framework allows to account for many complex phenomena which influence the respiratory process, like the nonlinear behavior of the underlying mechanical structure (parenchyma), inertial effects, the influence of the smooth muscle, surface tension … This chapter is of central importance in this book: it can be read without any prior knowledge of the underlying phenomena, with minimal mathematical background.We placed it at the beginning of this book, thereby favoring a Top Down approach; but it also expresses in a condensed way a large part of what is contained in other chapters.

The next level of description (Chapter 3) consists in addressing the tree-like structure of the respiratory tract, with possible account of non-homogeneous perturbations (variables like pressure or flux may take different values within a generation). We shall define in a precise way the notion of global resistance, and introduce a mathematical object corresponding to the ventilation process, which consists in prescribing negative pressures at the leafs of a resistive tree to trigger air flow through the tree.

We will enter the Partial Differential Equation framework in Chapter 4, giving an overview of the problems raised by attempting to model the motion of a fluid obeying the Navier-Stokes equations in an "open" domain, i.e. with inlet/outlet boundaries. This concerns the upper part of the respiratory system, where the so called *Reynolds* number, which quantifies the importance of inertial effects and thereby the nonlinear character of the flow, is high. Beyond the theoretical problems raised by the fact that the system is not closed (kinetic energy is likely to enter or exit the system), we shall focus on the different ways that have been proposed in the Bioengineering literature to couple the Navier-Stokes model with alternate ones, possibly lower dimension models. We shall then describe the various ways to articulate the different levels of descriptions presented previously, and address the theoretical and numerical issues raised by this multi-model description of the respiratory system.

In Chapter 5, we present various models to account for oxygen transfer from air to blood. Again, as direct modeling is ruled out by the geometrical complexity, we propose different levels of description that balance between numerical tractability and accurate modeling of the underlying phenomena.

Chapter 6 collects some developments that are a bit further from the modeling of the real lung. In particular we investigate the possibility to define an infinite counterpart of the actual respiratory tract. As we shall see, such an object can be extrapolated directly from the actual respiratory tract, and it sheds an interesting light on the mathematical nature of the ventilation process. It also allows to design a new type of fluid-structure interaction problem to represent the overall ventilation process. This model will be obtained by embedding the ends of our infinite tree into a Euclidean domain (the parenchyma), and considering that any local change in volume in the structure induces some flow through the tree, therefore some dissipation.

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