Applied Mathematical Models in Human Physiology

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Preface

The purpose of this book is to study mathematical models of human physiology. The book is a result of work by Math-Tech (in Copenhagen, Denmark) and the BioMath group at the Department of Mathematics and Physics at Roskilde University (in Roskilde, Denmark) on mathematical models related to anesthesia simulation. The work presented in this book has been carried out as part of a larger project SIMA (SIMulation in Anesthesia)\(^1\), which has resulted in the production of a commercially available anesthesia simulator and several scientific research publications contributing to the understanding of human physiology. This book contains the scientific contributions and does not discuss the details of the models implemented in the SIMA project.

In order to develop an anesthesia simulator it is necessary to model many aspects of the physiology in the human body. This book is devoted to presenting models reflecting current research relevant to cardiovascular and pulmonary physiology. In particular this book presents models describing blood flow in the heart and the cardiovascular system, as well as transport of oxygen and carbon dioxide through the respiratory system. The models presented describes several aspects of the physiology and it is our hope that this book may provide inspiration for researchers entering this area of study, and for advanced undergraduate and graduate students in applied mathematics, biophysics, physiology and bio-engineering. Each of the chapters present a unique model that can be read independently of the other chapters.

Chapters 5 and 6 have been used in graduate level courses in applied mathematics at Roskilde University, at Boston University, and at North Carolina State University. Moreover, most of Chapters 2-8 have been used in project organized and problem based student activities at graduate and advanced undergraduate levels at Roskilde University. When using the book in a traditional organized course, we suggest that the students use the models as a collection of examples that can serve as inspiration in their own modeling. Since we find it important that, in a modeling situation, students are involved in both formulating and solving problems we have not included traditional exercises at the end of each chapter.

The mathematical background used to derive our models is not presented in detail in this book, however, each chapter includes references to pertinent background material. It is expected that the reader has some knowledge of ordinary and partial differential equations, which are used in the models and are solved using numerical methods. The equations are not subject to analytical mathematical scrutiny, therefore a limited understanding of the methods underlying the use of these equations is sufficient. In addition, it is expected that the reader has a basic knowledge of physiology. We provide a chapter summarizing the main physiological results necessary for understanding the modeling assumptions and methodologies.

The introduction discusses the different levels of models presented in this book. Some models are simple “real-time” models that can be directly used in larger systems, while others are more detailed “reference” models that the reader can use to obtain a better understanding of the underlying physiological mechanisms, and to provide parameters for and validation of simpler models. The second chapter presents an overview of aspects of cardiovascular and pulmonary physiology necessary for understanding the model assumptions and limitations used throughout the remaining chapters. Most of the information in this chapter is taken from standard textbooks in physiology, supplemented with more advanced concepts that are needed for modeling.

Chapters 3 to 8 describe six different models of the cardiovascular and pulmonary systems. These six models can be studied individually, so the chapters may be read in any order. Each chapter may be used as a separate case study of the relevant subject. We have chosen to present the chapters in the order that we find most natural with respect to human physiology. Chapter 3 presents a two-dimensional model of the pumping heart that is based on the Navier-Stokes equations. It describes contraction and blood flow through the left ventricle of the heart. The results obtained from the model are compared with data obtained from Magnetic Resonance Imaging. Chapter 4 continues the discussion of the heart and presents a model describing the heart as a pressure source depending on time, volume and flow. The model offers a separation between isovolumic (isolated) and

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\(^1\) SIMA comprises the Danish contribution to the Eureka project HPPC/SEA EU 1063 that ran from 1994 to 1998.
ejecting heart properties, a modeling approach that contrasts with traditional time-varying elastance models. After discussing the heart we describe cardiovascular circulation using three models: a one-dimensional model that is able to predict blood flow and pressure at any location along the large systemic arteries (in Chapter 5) and two zero-dimensional models (in Chapters 6 and 7) that provide flow and pressure at a number of discrete locations in the entire cardiovascular system, including the heart, the systemic and pulmonary arteries, and the veins. The one-dimensional model is based on the Navier-Stokes equations with a constitutive equation relating pressure to the cross sectional area of the vessels. The second model in Chapter 7, which describes baroreceptor control of blood pressure is based on the circulatory model described in Chapter 4. After discussing the pumping heart and the circulatory system, the last chapter of the book (Chapter 8) presents a model of the respiratory system, which describes the exchange of the respiratory gases O\textsubscript{2} and CO\textsubscript{2}, using a mechanical lung model and a blood transport model. In addition, an elaborate model of bloods pH-value is also presented.

The editors wish to thank professor Stig Andur Pedersen at the Department of Philosophy and Science Studies at Roskilde University for starting the SIMA simulation project and the BioMath group at the Department of Mathematics and Physics at Roskilde University. We also thank professors James Keener, James Sneyd, and Clyde Martin for reading this book and providing essential comments and suggestions. In addition we wish to thank Heine Larsen at Systematic and Denis Thompson at the BioMath Program at North Carolina State University. We thank Mr. Larsen for technical support with putting this book together. Without Mr. Larsen we would not have been able to keep track of the newest version of texts, figures, and tables. We thank Mr. Thompson for revising this manuscript and improving the readability. This book is a result of collaborative work between the authors and editors, and as editors we have shared the work in getting this book finished. It is our hope that through these case studies, this book can serve as a background for discussions and provide new ideas for anybody interested in physiological modeling.

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5 Modeling Flow and Pressure in the Systemic Arteries 77

5.1 Structure of the Large Arteries 80
5.1.1 Geometric Properties of the Large Arteries 80
5.1.2 Structural Properties of the Vessel Walls 81
5.2 Structure of the Small Arteries 82
5.2.1 Radius and Asymmetry Relations 85
5.2.2 Order of the Structured Tree 86
5.2.3 Length of Segments 86
5.2.4 Wall Thickness and Young’s Modulus 86
5.3 Fluid Dynamic Model of a Large Artery 86
5.3.1 Momentum and Continuity Equations 87
5.3.2 State Equation 91
5.4 Flow and Pressure in the Tree of Large Arteries 92
5.4.1 Inflow Condition 93
5.4.2 Bifurcation Conditions 93
5.4.3 Outflow Condition 94
5.5 Fluid Dynamic Model of a Small Artery 95
5.5.1 Momentum Equation 96
5.5.2 Continuity and State Equations 97
5.5.3 Solutions to the Linear Model 97
5.6 Impedance at the Root of the Structured Tree 98
5.6.1 Bifurcation Condition 98
5.6.2 Outflow Condition 98
5.6.3 Root Impedance of the Structured Tree 99
5.7 Results 101
5.7.1 Model Problem 101
5.7.2 Structured Tree Model, windkessel Model, Pure Resistance Model, and Measured Data 104
5.8 Conclusion 108
5.8.1 Perspectives 110
5.8.2 Pathological Conditions 111

6 A Cardiovascular Model 113

6.1 Architecture of Cardiovascular Models 113
6.2 Cardiovascular Model 115
6.2.1 Heart 115
6.2.2 The Vasculature 117
6.2.3 Determination of Parameter Values 117
6.2.4 Computed Results 118
6.3 The Cardiovascular Model in Equations 121
6.4 Parameter Values 124

7 A Baroreceptor Model 127

7.1 Control Mechanisms of Human Circulatory System 128
7.2 Baroreceptor Mechanism 128
7.3 Afferent Part 129
7.3.1 Models of the Firing rates 130
7.3.2 The Unified Models 131
7.4 CNS and the Efferent Part 133
7.5 Open Loop Descriptions of the Baroreceptor Mechanism 134
7.5.1 Estimation of the Distributed Time Delay 135
8 Respiration
8.1 Introduction .................................................. 155
8.1.1 Lung Modeling ........................................... 155
8.1.2 Blood Gas Transport ..................................... 157
8.2 Modeling the Lung ........................................... 158
8.2.1 Pressure Model ........................................... 159
8.2.2 Gas Model ................................................ 163
8.2.3 Parameters in the Lung Model ......................... 166
8.3 Models of the Blood Transport System ................... 168
8.3.1 Mass Balance Equations ................................. 168
8.3.2 Metabolism .............................................. 173
8.3.3 Gas Dissociation and pH Value ......................... 174
8.3.4 Models of Gas Dissociation and pH Value ............. 176
8.3.5 Control of Respiration ................................ 180
8.4 Results ....................................................... 181
8.4.1 Lung Model .............................................. 182
8.4.2 Dissociation Curves .................................... 185
8.4.3 Blood Transport Model ................................. 190

A The SIMA Simulator ........................................... 195
A.1 Anesthesia simulation ..................................... 195
A.2 The models of SIMA ....................................... 196

B Momentum Equation for a Small Artery ..................... 201
B.1 Motion of the Fluid ......................................... 201
B.2 Motion of the Vessel Wall ................................. 201
B.2.1 Internal Forces .......................................... 202
B.2.2 External Forces ......................................... 203
B.2.3 Balancing Internal and External Forces ............... 205
B.3 Elasticity Relations ........................................ 207
B.4 Balancing Fluid and Wall Motions ....................... 207
B.5 Linearization ............................................... 207
Chapter 1

Introduction

J.T. Ottesen, M.S. Olufsen, and J.K. Larsen

This book is about mathematical modeling of human cardiovascular and respiratory physiology at the systems level. In the introduction we give some background on the advances in the field through examples mainly drawn from our own experience and through a discussion of the modeling process. The field of mathematical cardiovascular and respiratory physiology is so vast that it is not possible to give a thorough description of all aspects in one book. For a general introduction to the subject we recommend the book by Hoppenstadt and Peskin (Hoppenstaedt and Peskin, 1992), which includes a thorough introduction to processes involved in setting up realistic models that obey physical laws and describe the underlying physiology. A more comprehensive and more advanced treatment of mathematical physiology can be found in the book by Keener and Sneyd (Keener and Sneyed, 1998).

1.1 Background

The interdisciplinary field of applied mathematical modeling in human physiology has developed tremendously during the last decade and continues to develop. One of the reasons for this development is researchers’ improved ability to gather data. The amount of physiological data obtained from various experiments is growing exponentially due to faster sampling methods and better methods for obtaining both invasive and non-invasive data. In addition, data have a much better resolution in time and space than just a few years ago. For example, some of the non-invasive measurements using MRI (magnetic resonance imaging) can provide information of blood velocity as a function of time and three spatial coordinates in both the heart and in arteries with a diameter of only a few millimeters. Another recent accomplishment is the ability to image neural activity in the brain by studying the changes in the oxygen level in the capillaries. These studies do not depict single vessels but small regions.

This large amount of data obtained from advanced measurement techniques constitute a giant collection of potential insight. Statistical analysis may discover correlations, but may fail to provide insight into the mechanisms responsible for these correlations. However, combined with mathematical modeling of the dynamics new insights into physiological mechanisms may be revealed. The large amount of data can make the models give not only qualitative but also quantitative information of the function they predict and they may also be used to suggest new experiments. We think that such models are necessary for improving the understanding of the function of the underlying physiology, and in the long term mathematical models may help in generating new mathematical and physiological theories. Some examples are: modeling the time-delay related to the baroreceptor mechanism may lead to suggestions for what could be responsible for Mayer waves (certain oscillations in the mean arterial pressure) (Ottesen, 1997a). Modeling the propagation of the pulse wave along the aorta may explain the presence of the dicrotic notch in the pulse profile and how the dicrotic notch changes along the aorta (Olufsen and Ottesen, 1995b; Olufsen and Ottesen, 1995a; Olufsen, 1999; Olufsen, Peskin, Larsen and Nadim, 2000). Modeling the dynamics of cerebral blood flow response to sudden hypotension during posture change from sitting to standing may provide a better insight into cerebral autoregulation (Olufsen, Nadim and Lipsitz, 2002). Other examples can be found in the recent book by Keener and Sneyd (Keener and Sneyed, 1998).

In addition, models can help to avoid confusions, misunderstandings and wasted effort. Most if not all concepts can be clearly defined only by the use of mathematics. Without mathematical descriptions, obscurity and ambiguity will arise sooner or
Such ambiguity was seen, for example when a few researchers separately proposed different single indices characterizing the contractile state of the ventricle. Some of these indices depend on the vascular system in an essential way, thus instead of characterizing the contractile state of the ventricle they characterized the interaction between the ventricle and the vascular system (Danielsen and Ottesen, 1997; Danielsen, 1998; Ottesen, Danielsen, Palladino and Noodergraaf, 1999; Danielsen and Ottesen, 2001).

Likewise the use of mathematics often provides a tool for structuring thoughts for the researchers who create the model and the ones who use it. For example, when a vein is occluded during surgery, the resistance to the blood flow is increased and as a result a fall in cardiac output is usually observed. However, even though cardiac output usually falls there are cases that show the opposite response: an increase in cardiac output. This apparently inconsistent response to the occlusion of veins is not understood by most physicians. The inconsistent responses make sense in light of the topology of the cardiovascular system model: while occluding the supply to a highly compliant organ causes an increase in cardiac output, occluding the supply to regions with low compliance causes a decrease in cardiac output (Ottesen, 2000).

Another point is that mathematical models frequently generate new and very important questions that could not be asked without the use of mathematical models. Examples are: how does the topology of the vascular system influence the function of the system? Are vortices, which are created on the downstream side of the aortic valves when blood is ejected from the ventricle, responsible for the subsequent closing of the valves? If so can these valves close without any blood flowing back into the ventricle? What is really meant by the phrase “contractility of the ventricle”, and do people use this phrase consistently? Can hysteresis and other non-linear phenomena of the baroreceptor nerves be caused by a single mechanism? Under what conditions is the cardiovascular system stable? Will minor perturbations in function cause only minor changes in the state of the cardiovascular system? How much can the function of the baroreceptor feedback mechanism, which controls how heart rate responds to arterial pressure, vary without vital failure? What factors are responsible for the creation of the dicrotic notch in the pulse profile? Why does the dicrotic notch change along the aorta? These and many other questions are easy to describe and they make perfect sense to people who are not mathematically oriented. However, upon closer scrutiny the questions above reveal that the exact meaning of single words or of the systems involved are based on particular mathematical models. In any case all of the above questions are direct results of mathematical models even though the underlying models are not mentioned explicitly.

Finally, the ongoing development of mathematical modeling in physiology has increased the use of models (and the insights they offer) in the medical industry. This is an area that in engineering has been used for decades. For example who would imagine a pilot of a freight ship or an airplane that has not had extensive training in a simulator? However, the surgical team in an operating theater has usually not had training in a simulator - neither has the surgeon used a simulator for training or planning of the surgery nor have the anesthesiologists trained to react to these rare events of reactions to anesthesia that may be fatal if not treated within minutes. Finally, the doctors, nurses, and technical personnel, have not usually had any simulated training in how as a team to operate the very advanced technical monitoring equipment. The wish to establish a solid foundation for the development of an anesthesia simulator has been the main inspiration for the work described in this book. Appendix A has a short description of the anesthesia simulator SIMA (SIMulation in Anesthesia) that is based on the models reported in this book.

1.2 Mathematical modeling

This book will discuss various models of human physiology, simple as well as more detailed models that can be used to obtain a better understanding of parts of the underlying systems. The models described in this book are based on fundamental physical laws and a goal has been to achieve models that reflect correct qualitative and quantitatively behavior. All of the models discussed in this book have been derived using advanced mathematics and the quantitative results are obtained from implementing the models using a numerical approach where parameters have been estimated based on experimental measurements. As a result the models require a computer system to run.

As described above, the inspiration for this book has been the development of an anesthesia simulator. This inspiration has inspired the development of two levels of models: comprehensive models that that adequately describe the physiology in a detailed way, but that cannot run in real time; and simple models that utilize the understanding obtained from the comprehensive models, but that are modified such that they can run in real time. When developing an anesthesia simulator it is important to have models that can run in real time, hence distinguish between the two levels of models.

The comprehensive models will be referred to as reference models and the simpler models as real-time models. The aim
of this book is to describe these models, to show the importance of the two levels of models, and to give an idea of how to implement real-time models. Even though the reference models presented here are only a small subset of possible physiological models, they still represent the framework for building and validating simple models that has to run in real time.

Development of models with different layers of complexity reflects the difficulties that arise during scientific analysis of objects and phenomena as they appear to us in daily life. Such objects are often too complex and vaguely defined to be accessible to scientific scrutiny. As a result the objects must be delimited and prepared in such a way that scientific concepts are applicable. This is a relatively complex process in which a concrete object is transformed into a generalized generic object that we may call the model object. Definition and interpretation of such objects is performed with some purpose in mind, that will give rise to a certain level of detail in a derived mathematical formulation. For example consider the transport model in Chapter 8. This model describes the transportation of various substances such as oxygen or anesthetic agents in the human body. In order to develop such a model one must think of a generic human body in two distinct ways: As an average human being and as a simplified and idealized object. One simplification is that blood is a homogeneous fluid. Another is that various body tissues can be grouped together into a few compartments, e.g. in the respiratory model described in Chapter 8, the complex branching of the airways are lumped into four compartments depending on the diameter of the airways. In this way we think of the human body not as it is in reality, but as an idealized and simplified object. All measurements and mathematical models use such idealized versions of real objects.

It is important to notice that physical measurements always must be interpreted based on a set of assumptions that makes sense relative to the model object. For example, when an invasive blood pressure is measured in a large artery it is assumed that the catheter is placed in a smooth laminar blood stream and that the blood is a well-behaving incompressible fluid. Impurities and interfering features are eliminated or included in a negligible amount of noise. Furthermore, fundamental laws of nature only hold for generic model objects and not for objects as they are in themselves. Consider, for instance, the incompressible Navier-Stokes equations. They can be derived from the Boltzmann equation of non-equilibrium statistical mechanics (Bardos, Golse and Levermore, 1991) under some simplifying assumptions: that the flow field varies only in length and time scales much greater than the microscopic scales associated with the mean free path and mean free time of particles, and that velocities are much less than the speed of sound. Therefore, when we apply Navier-Stokes equations we tacitly assume that our fluid is a system of particles complying with such general assumptions. These equations are studied in detail in Chapters 3 and 5.

Consequently, when we embark on the task of building a mathematical model of a physiological process in accordance with fundamental laws, we have already made far-reaching generalizations. We are considering a generic human being as a model object. However, in order to construct a mathematical model which is computationally accessible we must make even more radical idealizations and simplifications. As an example, consider the arterial tree. When a clinician is measuring the blood pressure somewhere in a large artery it is assumed that there is a definite well-defined pressure at that place, e.g. that the blood flow is regular and smooth enough to allow a well-defined pressure. But when we want to construct a mathematical model of the arterial tree which can predict pressure and flow profiles we must make a series of simplifications. First, we must make the assumptions underlying the Navier-Stokes equations. Second, we must simplify the arterial tree such that we have a manageable number of equations. Finally, the equations must be simplified so they are accessible to numerical solution. An example of such a model is discussed in Chapter 5.

When so many simplifications and idealizations are made when creating a manageable model, how can one have confidence in its validity? How can we be sure that the model still complies with basic laws? And how is it possible to compare the model, which describes a general model object, with physiological data? We shall not go into a full discussion of these problems here. But we emphasize that in our reference models all simplifications are made in such a way that basic laws, e.g. mass and momentum conservation, are not violated. Furthermore, we do not claim that our models are able to give detailed numerical predictions, but only that they account for the principal qualitative behavior of the system being modeled. And it is that principle qualitative behavior the model assists the underlying understanding. The understanding obtained from these detailed models can bee carried over to the more simple models that can be directly used in a larger system. Even for these real time models, our goal is that they obey fundamental physical laws. However, achieving that goal is not always possible when creating a large realistic system. So in cases where it is not possible to develop physical models it becomes necessary to use shortcuts based on empirical, statistical, or even simple profile models.

The strategy outlined for building models of large physiological systems has been applied in the development of the anesthesia simulator SIMA. This development has been an interdisciplinary process involving mathematical modeling, physiological experimentation, numerical analysis, and design of hardware and software interfaces. Although it has been necessary to make compromises at vital points, the process has shown that it is possible to develop a full scale anesthesia simulator based, at essential points, on realistic mathematical models of physiological processes. Our use of a combination of real-time models
and reference models has been instrumental to our successes. We believe that many researchers in the mathematical, biological, physical, and biomedical communities would find this approach useful.

Bio-medical modeling is an important discipline which has gained new impetus due to new developments in computer technology and mathematical modeling. By building better reference models and improving the existing ones it is possible to develop advanced simulation environments which are essential for education and research, leading to a deeper understanding of human physiology.

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Chapter 2
Cardiovascular and Pulmonary Physiology
and Anatomy

M.S. Olufsen, M. Danielsen, P.T. Adeler, and J. Larsen

In order to develop a physiologically correct model of an aspect of the cardiovascular or pulmonary system, one must understand relevant parts of the underlying physiology. This book describes a number of models which model aspects of the heart, cardiovascular, and pulmonary systems. The background physiological knowledge upon which these different models are based overlaps, so this background physiology is covered together in this chapter. Most of the material in this chapter can be found in basic physiological textbooks such as, “Textbook of Medical Physiology” by AC Guyton (Guyton, 1991), “Principles of Human Anatomy” by GJ Tortora and NP Anagnostakos (Tortora, 1999), “Human Anatomy and Physiology” by EP Solomon et al., “Review of Medical Physiology” by WF Ganong (Ganong, 1975), and “The Mechanics of the Circulation” by Caro et al. In addition to these basic physiological facts however, this chapter includes more subtle details necessary for understanding all aspects of the model. Readers with sufficient physiological knowledge can skip this chapter and go directly to the modeling chapters. However, readers without sufficient physiological knowledge will benefit from reading this chapter before reading the modeling chapters.

This chapter does not present an overview of all parts of the cardiovascular and pulmonary physiology, rather, it gives an overview of the parts relevant for the subsequent modeling chapters. Section 2.1 gives an introduction to the organization of the cardiovascular system. Section 2.2 offers an overview of the basic physiology and anatomy of the heart. The physiology of the systemic arteries is described in Section 2.3 and Section 2.5 gives an introduction to pulmonary physiology.

2.1 Cardiovascular Physiology

The human cardiovascular system is primarily a transport system in which oxygen, carbon dioxide and nutrients are carried by the blood to and from the various muscles and organs. The cardiovascular system consists of two separate parts; the systemic circuit and the pulmonary circuit.

These two parts are connected via the heart. From the left ventricle blood is pumped into the systemic circuit through the aorta (the largest artery in the body). The systemic arteries transport oxygen and nutrients to the various muscles and organs. At the capillary level oxygen and nutrients diffuse from the vessels into the muscles and organs. In the muscles and organs oxygen is partially exchanged with carbon dioxide and as a result the blood becomes partly de-oxygenated. From the capillaries blood is discharged into the venules and then into the veins. Finally, through the vena cava (the largest vein in the body) blood is transported to the right atrium and from there to the right ventricle. The right ventricle pumps blood into the pulmonary circulation in which the partly de-oxygenated blood is carried to the lung tissues, where carbon dioxide is exchanged with oxygen in the alveoli. Subsequently, the nearly re-oxygenated blood is carried back to the left atrium and from there back into the left ventricle. Thus blood makes a complete trip through both circuits.

The systemic and pulmonary circuits exhibit significant differences in terms of blood pressure and blood volume. The pressure in each circuit are shown in Figure 2.2. In addition, the figure shows the approximate minima, maxima, and average pressures obtained during each cardiac cycle, at different locations of the cardiovascular system. The maximum and minimum pressures in the systemic aorta are approximately 120 mmHg and 80 mmHg, respectively. The corresponding pressures in the
Figure 2.1: The circulatory system. From Tortora and Anagnostakos (1990).
pulmonary arteries are 30 and 10 mmHg. The veins exhibit the lowest pressures. In the venules the pressure oscillates around 10 mmHg. Oscillations in the pulmonary veins are more profound. The volume of blood in the pulmonary circulation (in the pulmonary arteries and veins) comprises approximately 14% of the total blood volume. The volume in the systemic circulation is 74% of the total volume. At any given time approximately 54% of the blood is in the veins, 20% is in the arteries and 12% is in the heart, see Table 2.1.

<table>
<thead>
<tr>
<th>Location</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arteries</td>
<td>20%</td>
</tr>
<tr>
<td>Systemic veins</td>
<td>54%</td>
</tr>
<tr>
<td>Pulmonary circuit</td>
<td>14%</td>
</tr>
<tr>
<td>Heart</td>
<td>12%</td>
</tr>
</tbody>
</table>

Table 2.1: Volume distribution in the cardiovascular system relative to the total volume (Ganong, 1975; Noordergraaf, 1978).

### 2.2 The Heart

The heart is considered to be the only source of energy that moves blood in the circulatory system. However, the heart is not an independent pump but a complex organ affected by the rest of the cardiovascular system. Consideration of the detailed structure of the heart may further one’s understanding of this interaction. Therefore, this section offers an introduction to the anatomy of the heart, its conduction system, and the physiology of its muscles.

#### 2.2.1 The Cardiac Cycle

As shown in Figure 2.3 the heart consists of four chambers split between the two sides. Each side has a ventricle and an atrium. The left ventricle and left atrium are connected via the mitral valve, which during normal conditions prevents flow from the ventricle into the atrium. The right ventricle and the right atrium are connected via the tricuspid valve. In addition to the valves between the heart chambers, each chamber has a valve connecting the arteries and veins to the heart. The aortic valve is positioned at the outflow from the left ventricle. At the outflow from the right ventricle is the pulmonary valve. A more detailed description of the internal anatomy is given in Section 2.2.2.

The time course of the cardiac cycle can be divided into an active phase and a relaxed phase. At the onset of the active phase, electrical stimulation causes the ventricular muscles to contract. As a result, ventricular pressure increases isovolumically (i.e. with no inflow and non-ejecting) until the ventricular pressure equals the arterial pressure. At this point the aortic valve opens (onset of systole) and blood flows into the aorta. During systole, ventricular pressure rises and falls as dictated by muscle
Cardiovascular and Pulmonary Physiology and Anatomy

Figure 2.3: The four chambered heart is divided into two separated parts, the left and the right sides. Both parts consist of a ventricle and an atrium. The left side of the heart is anatomically larger than the right side, see Section 2.2.2. From Rideout (1991).

contraction and prevailing conditions in the vasculature. The aortic valve closes (ending systole) when ventricular pressure drops below the arterial pressure and initiates an isovolumical relaxation phase. When the ventricular pressure falls below the atrial pressure, the mitral valve opens and blood flows from the atrium into the ventricle. This non-ejecting period is denoted diastole. The left atrium follows a similar track. The left atrium is filled from the pulmonary circulation during systole and supplies the ventricle actively with blood during diastole. However, only 30% of the ventricular filling (both for the right and the left ventricles) is due to the atrial contraction. The remaining 70% of the filling occurs during diastole. The amount of blood ejected by each ventricle, per stroke, is about 70 ml. The ejection fraction, the percentage of the ventricular volume ejected at each stroke, is about 65%. The duration of the cardiac cycle is approximately 0.8 sec during rest. The amount of blood ejected from the left ventricle into the ascending aorta is called cardiac output. In an resting adult the cardiac output is approximately 5 l/min (70 ml × 72 beats/min). Figure 2.4 shows the ventricular pressure and flow curves, representative for a normal left ventricle.

2.2.2 Internal Anatomy

As described above, the heart has four chambers (two atria and two ventricles) divided between two sides (left and right). The left and right side of the heart are separated by a septum. The atria are divided by the interatrial septum and the ventricles are separated by the interventricular septum. The atrioventricular openings connect the atrias and ventricles. This opening is surrounded by a ring of fibrosus tissue, the annulus fibrosus. The lower part of the heart is called the apex while the base refers to the opposite, broad, end of the heart, see Figure 2.5.

The heart walls consist of muscle tissue called the myocardium. The thickness of the myocardium varies over the heart and increases with workload. The atria do less work than the ventricles. Consequently the atrial wall is thin, approximately 2 mm. The right ventricle is exposed to the pressure of the pulmonary circulation and has a higher wall thickness, approximately 5 mm. The highest amount of work and hence the highest wall thickness, approximately 15 mm, belongs to the left ventricle, which ejects blood into the systemic circulation.
Due to the two sets of valves, the atrioventricular valves and the semilunar valves blood flow in the heart is unidirectional. The atrioventricular valves are located between each atrium and ventricle. The semilunar valves are found in the opening between each ventricle and artery. Valves are not found at the venous inlets into the atria, see Figure 2.5.

The atrioventricular valves consist of leaflets (cusps) with a triangular shape. The right heart chamber contains three leaflets and consequently the valve is denoted the tricuspid valve. The valve in the left chamber contains two leaflets and is thus referred to as the bicuspid valve (or the mitral valve). Leaflet tendons are found under each valve, also called the chordae tendineae. They originate from the papillary muscles that are located on the inner surface of each ventricle. When the atrium contracts the leaflets hang slack into the ventricle, but when the ventricle contracts the leaflets are pushed together, closing the atrioventricular opening. The chordae tendineae secure the leaflets preventing them from moving into the atrium during the contraction of the ventricle.

The semilunar valves prevent blood from flowing back into the heart after ejection into the arteries. Each of the semilunar valves consists of three crescent shaped leaflets. These leaflets have no chordae tendineae. They are dilated with blood and
close the opening when the pressure in the artery exceeds the pressure in the ventricle. The right semilunar valve is also called the pulmonary valve. The corresponding valve on the left side is called the aortic valve.

2.2.3 Conduction System of the Heart

Contraction of the heart is initiated by electrical stimulation. Electrical impulses are spread to all parts of the myocardium by the conduction system. The conduction system consists of the sinoatrial (SA) node, the atrioventricular (AV) node, the atrioventricular bundle (or bundle of His), the bundle branches, and conducting fibers called Purkinje’s fibers, see Figure 2.6. All parts of the conduction system are able to send out periodic impulses without neural stimulation. This lack of reliance on outside control is called automatism.

The SA node is a small mass of muscular fibers located in the myocardium of the right atrium near the inflow of the superior vena cava, see Figure 2.6. The SA node generates impulses faster than the other parts of the conduction system and thus initiates each heartbeat and controls the frequency of the heart rate.

The impulses from the SA node reach the atria first, causing them to contract. Much later the impulses reach the AV node, which is located in the interatrial septum, see Figure 2.6. The AV node is slowly conducting and thus the impulses are delayed in the AV node. This allows for the atria to empty their blood (by contraction) into the ventricles before the ventricles start to contract. From the AV node the impulses are sent through the bundle of His, which is the only electrical connection between the atria and ventricles. The bundle of His branches into two, one that goes to the right ventricle and one that goes to left ventricle. Both branches go in the direction of the apex of the heart and subdivide into a complex network of Purkinje fibers (see Figure 2.6). These fibers stimulate ventricular contraction, which starts at the apex and spreads superiorly towards the base of the heart.

2.2.4 Muscle Physiology

The heart pumps due to the contraction of its muscle fibers. Muscle fibers receive energy from biochemical processes and develop a force which manifests itself as an increasing cavity pressure.

Muscles in the heart lie in a complicated pattern which may be understood via the band concept introduced by Guasp (1980). The cardiac muscle itself consists of individual muscle fibers, or myocytes, that are the smallest functional units in the structure. Each muscle fiber is approximately $40 - 100 \mu m$ long with a diameter of $10 - 20 \mu m$.

Each muscle fiber contain a number of fibrils placed in parallel, see Figure 2.7. The fibrils have a characteristic striated
2.2 The Heart

Figure 2.6: The conduction system of the heart. From Tortora (1999).

Figure 2.7: Muscle fibers contain approximately 100 fibrils in parallel. The fibrils have a characteristic striated pattern which stems from the filaments, the interdigitating thick and thin filaments as indicated. The striated pattern is also shown in Figure 2.8. From Warberg (1995).

pattern. This pattern results from the parallel bundles of filaments, the interdigitating thick and thin filaments, lying between the Z-lines, see Figure 2.8. Filaments lie along the fibrils divided into approximately 50 \(2 \mu m\) blocks. A block is called a sarcomere and consists of approximately 1000 single thick-thin units of the type in Figure 2.8.

Figure 2.9 shows the sarcoplasmic reticulum between the fibrils in the muscle fiber. The sarcoplasmic reticulum contains a Ca\(^{2+}\) reservoir in the terminal cisternae which is essential during contraction. In addition, the muscle fibers contain T-tubules vital for conduction of action potentials to the sarcoplasmic reticulum, that release Ca\(^{2+}\) to the fibrils. The contraction of muscle fibers are explained by the sliding filament theory. This theory is the most widely embraced theory, and is based on a mechanical concept. But this theory is not the only one to explain muscle contraction. Rather than mechanical descriptions, other theories propose a field approach (Spencer and Worthington, 1960; Elliott, Rome and Spencer, 1970). The field approach has not enjoyed the same popularity since evidence exists in favor of a mechanical type (Noordergraaf, 1978). Accordingly, we will describe the fundamentals of the sliding filament theory.
Figure 2.8: Section of a fibril. The striated pattern follows from the bundle of filaments, the interdigitating thick and thin filaments shown in the middle panel in the relaxed state. A sarcomere is also indicated. The lower panel shows a single thick-thin unit with crossbridge bonds between thick and thin filaments. As crossbridge bonds attach between thick and thin filaments force develops with a concomitant increased overlap between the filament and diminished distance between neighboring Z-lines as indicated in the lower panel.

Figure 2.9: Part of a single muscle fiber with the sarcoplasmic reticulum. The T-tubule runs through the muscle fiber in a transverse direction through the fiber. Ca^{2+} is released from the terminal cisternae and diffuses into the fibrils. From Warberg (1995).

**Sliding Filament Theory**

In the 1950’s it was observed that the thick filaments remained in a stable suspension during contraction whereas the distance between neighboring Z-lines diminished. This observation led to the sliding filament theory, which states that the thick and thin filaments slide during contraction, changing the overlap between them. Sliding is accomplished by mechanical connections between thick and thin filaments which induce thin filaments to move with respect to thick filaments. The connections are called crossbridge bonds or bonds. During contraction, crossbridge bonds attach from the thick and thin filaments. According to the sliding filament theory crossbridge bonds continue to attach, push off, and re-attach. However, not all filaments continue to push off and re-attach, some simply stay attached. As a result of attachment, force is developed and the distances between
neighboring Z-lines are diminished with a concomitant increased overlap between the filaments as shown in Figure 2.8.

The formation of crossbridge bonds yields a rise of biochemical energy which in turn results in development of a force. The force continues to increase until the crossbridge bonds detach in sufficient high numbers. At this point, the force decreases and the muscle starts to relax. After a bond has detached it can attach again during the same contraction (cycling of bonds). At the chamber level ventricular pressure increases during formation of bonds between thick and thin elements and decreases during detachment of bonds.

Biochemical Energy

In the sliding filament theory, force is assumed to develop from a combination of mechanical and biochemical processes. In short this sequence of events can be described as follows. The available biochemical energy is closely related to the amount of Ca\(^{2+}\) while the actual release of energy stems from interaction between the proteins in the filaments. Thick filaments consist mainly of the protein myosin and thin filaments of the protein actin. During contraction the fibrils are electrically activated in the direction of the axes, and in the radial direction by the T-tubule. This electrical activation promotes release of Ca\(^{2+}\) near the Z-lines from the sarcoplasmic reticulum. After the release, Ca\(^{2+}\) binds to the protein troponin. Troponin sits on tropomyosin which wraps around actin molecules in the thin filaments. Troponin inhibits reaction between myosin and actin but the Ca\(^{2+}\) binding promotes structural changes which release this inhibition. Subsequently, myosin interacts with actin via the crossbridge bonds and releases energy. Shortly after Ca\(^{2+}\) is pumped back to the sarcoplasmic reticulum which requires energy and takes time, longer than starting of the contraction. This enhances inhibition of the actin-myosin interaction and thus formation of new bonds. Eventually force decreases and the muscles relax.

2.3 Systemic Arteries

The systemic arteries are composed of large arteries, smaller arteries, and arterioles, see Figure 2.10. Their topological pattern forms a vast network of branching vessels. The total cross-sectional area increases from 5 cm\(^2\) at the root of the aorta (the biggest artery) to approximately 400 cm\(^2\) at the entrance to the arterioles, see Table 2.2. These numbers should be seen as orders of magnitude because it is impossible to measure the area of the arterioles precisely. Consequently, there is a considerable variation in the tabulated values given in different textbooks of physiology (Guyton, 1991; Gregg, 1966; Caro, Pedley, Schroter and Seed, 1978).

![Cross-sections of arteries and veins](figure2_10.png)

Figure 2.10: Cross-sections of arteries and veins. The vessels have an inner layer of endothelial cells and an outer layer composed of fibers with a varying degree of muscle and elastic fibers. The figure shows the relative content for each group of vessels. From Li (1987).

The diameters of blood vessels range over several orders of magnitude. This variation may impose a problem for modeling purposes, but that problem can be overcome by dividing the arteries into several groups: large arteries, small arteries, arterioles and capillaries. This distinction is somewhat arbitrary, but can be justified by the different properties of the vessels as they gradually become smaller.
The large systemic arteries are characterized by strong, highly elastic, vascular walls. The walls of the small arteries are less elastic. The walls of the arterioles and capillaries are almost rigid and contain more smooth muscle than the walls of the aorta, large arteries, and small arteries. This musculature will be described in detail in Section 2.3.1. It is the change in wall properties, together with the vast expansion of the network, that enables a significant drop in blood pressure and flow at the arteriolar level. The most important regulation of blood flow is in the arterioles. They act as control valves through which blood is released into the capillaries. For this function, they have strong muscular walls that can constrict the vessels completely or dilate them severalfold. The purpose of varying the cross-sectional area of the arterioles is to alter the blood flow into the capillaries in response to the needs of tissues. The resistance resulting from this behavior is often referred to as the peripheral resistance.

In contrast to the arterioles, the capillaries contain no muscles. Until the capillary level the branching of blood vessels is mostly binary (e.g. in the coronary arteries and arterioles 98% of the bifurcations are binary (Kassab and Fung, 1995)). However, the capillary network extends into a huge “swamp” without a certain (e.g. binary) branching structure (for example capillaries branch in bifurcations, trifurcations, and contain many loops). The region has a high surface area and the flow is low and no longer pulsatile. The purpose of the capillaries is to exchange oxygen and nutrients between the blood and the interstitial fluid of the cells. (Or between the blood and alveoli in the case of the pulmonary circuit.) This diffusion is achieved through a slow and steady flow and it is mediated by the permeability of the capillary walls to small molecular substances. Since flow through the capillaries has to be steady and slow, another important role of the arteries is to damp the waves resulting from the pulsatile flow entering the aorta from the left ventricle. Again, this damping is achieved via a distal increase its cross-sectional area of the network, and the elasticity of the arteries.

As opposed to arteries, veins are low pressure vessels with a low flow, and their vessel walls are thin, with low elastic properties and resistance. The latter characteristic makes veins ideal for storage of blood, because large volume alterations can be achieved without significant pressure changes. The veins contain muscles which can move blood volume to other parts of the cardiovascular system. Furthermore, none of the arterial pulsations are transmitted into the veins. However, pulsations with other causes can be observed in the veins. These pulsations are due to either heart generated waves passing retrograde towards the periphery, or to respiratory fluctuations (O’Rourke, Kelly and Avolio, 1992).

The amount of blood ejected from the right ventricle into the pulmonary artery is slightly smaller (1–2%) than the amount ejected into the ascending aorta. The reason for this difference is that the oxygenated blood needed to supply the lung tissues is not returned to the right atrium but continues through the lung into the pulmonary veins. Then this blood continues in the pulmonary vein and enters the left atrium, rather than passing back through the systemic veins into the right atrium.

Seen from a mechanical point of view, this distinction makes perfect sense because blood flow in the arteries is significantly different than that in the arterioles. The difference can be explained in terms of the fluid mechanical characterization of the flow: If the flow has a Reynolds number significantly larger than one, it is dominated by inertia; if the Reynolds number

<table>
<thead>
<tr>
<th></th>
<th>Diameter (mm)</th>
<th>Wall Thickness (mm)</th>
<th>Cross-Sectional Area (cm²)</th>
<th>Percentage of Blood Volume Contained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>25</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Arteries</td>
<td>4</td>
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<td>20</td>
<td>8</td>
</tr>
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<td>0.03</td>
<td>0.02</td>
<td>400</td>
<td>1</td>
</tr>
<tr>
<td>Capillaries</td>
<td>0.008</td>
<td>0.001</td>
<td>4500</td>
<td>5</td>
</tr>
<tr>
<td>Venules</td>
<td>0.02</td>
<td>0.002</td>
<td>4000</td>
<td>5</td>
</tr>
<tr>
<td>Veins</td>
<td>5</td>
<td>0.5</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>Vena Cava</td>
<td>30</td>
<td>1.5</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2: Lumen diameter, wall thickness, approximate total cross-sectional area, and percentage of blood contained in the given group of arteries. The total volume of blood is not 100% since the table does not account for 12% blood in the heart and 18% in the pulmonary circulation (Gregg, 1966).
2.3 Systemic Arteries

is much smaller than one, the flow is dominated by viscosity. In the case of blood flow, the Reynolds number drops below one when the vessels diameter becomes less than 100 \( \mu \text{m} \). This diameter corresponds to the diameter of the larger arterioles, which range in size from 50–100 \( \mu \text{m} \). The diameter of the arterioles decreases by progressive bifurcations down to the smaller arterioles (sometimes called the met-arterioles) where the diameter is approximately 30 \( \mu \text{m} \), see Table 2.2. In addition, there is a functional difference between the two types of arteries. The purpose of the larger arteries is to distribute blood to the different muscles and organs, while the role of the smaller arteries and arterioles is to distribute blood (and, in the case of the arterioles, to control its distribution) within those muscles and organs.

The arteries and larger arterioles comprise a complex bifurcating tree. Henceforth we refer to it as the arterial tree. However, the met-arterioles do not have a bifurcating tree structure, instead multiple branches and loops often occur. The order of the arterial tree is large. Assume an arteriolar diameter of 30 \( \mu \text{m} \) and a total cross-sectional area of 400 \( \text{cm}^2 \), see Table 2.2. If we then construct a binary tree consisting of the aorta, the arteries, and the larger arterioles, it will have 26 generations. Even if we neglect the arterioles and only consider the larger and smaller arteries, i.e. those with a diameter larger than 100 \( \mu \text{m} \) (corresponding to 40 \( \text{cm}^2 \)), the tree will have as much as 19 generations. Such a tree cannot be depicted but the tree shown in Figure 2.11, where only the larger and a few of the smaller arteries are shown, is still highly complex.

2.3.1 Arterial Wall

The arterial wall is composed of variable amounts of elastic fibers and smooth muscle, enabling it to dilate when the pulse wave propagates along an artery. It is not purely elastic but exhibits some viscoelastic behavior. As a first approximation arteries are circular vessels tapering along their length. As mentioned in the previous section, arteries can be subdivided into the following three groups according to their elastic behavior:

- Elastic arteries which are the major distribution vessels, such as the aorta, the common carotid arteries, or the subclavian arteries.
- Muscular arteries (see Figure 2.12) which comprise the main distributing branches of the arterial tree. These include the radial or femoral arteries.
- Arterioles (see Figure 2.12).

The transition in structure and function in the arteries is gradual. Generally, the amount of elastic tissue decreases as the vessels become smaller and the smooth muscle component becomes more prominent (Wheater et al., 1987). Consequently, the arteries become markedly stiffer with increased distance from the heart. The parameters characterizing the elastic properties are Young’s modulus, which is greater for arteries farther away from the heart, and relative wall thickness, which is constant for the larger arteries, but increases for the smaller arteries and arterioles. The arterial wall is composed of three layers characterized by their predominant structure and cell types.

- The internal layer, the tunica intima, is composed of an endothelial layer and an outer elastic laminar layer. The endothelial layer comprises an inner layer consisting of a single layer of endothelial cells and an outer sub-endothelial layer. The single cell endothelial layer is present as a border to all surfaces that come in contact with the blood. It is rather fragile and is easily damaged e.g. by excessive shear rates. However, it also easily regenerates. The sub-endothelial layer contains a few collagen generating cells and collagen fibers. The elastic laminar layer consists of branching elastic fibers. It is particularly well defined in the smaller arteries where it forms a clear boundary to the middle layer.

- The middle layer, the tunica media, is the thickest layer in the wall. It is also the layer which has the greatest variation in structure and properties between different regions of the circulatory system. Transitions in the structure of this layer allow the division of arteries into the elastic and muscular categories. The tunica media of the elastic arteries is made of multiple concentric layers of elastic tissue separated by thin layers of connective tissue. Collagen fibers and sparse smooth muscle cells organized in a longitudinal way forming cross-links to the successive elastic layers. More details are given in Caro et al. (1978). In the corresponding layer of the muscular arteries, elastic tissue is reduced and the smooth muscle cells are dominant. These cells are oriented circumferentially in spiral structures.
• The external layer, the tunica adventitia, can be as thick or even thicker than the tunica media. However, it is less prominent microscopically. It is composed of loose connective tissues and relatively sparse elastin and collagen fibers, running in a predominantly longitudinal direction. The boundary with the surrounding tissue is often not well defined.

Figure 2.11: The arterial tree. From Solomon, Smidt and Adragna (1990).
Figure 2.12: The wall of a muscular artery (top) and a large arteriole (bottom). The muscular artery internal layer consist mainly of a thin elastic sheet (marked with IEL). The middle layer, tunica media (marked with an M) is composed mainly of smooth muscle. The outermost layer, tunica adventitia is composed of a diffusive external elastic lamina. In addition collagen fibers are scattered throughout the vessel wall. Arterioles have a thin internal layer which comprises a endothelial lining, little collagenous connective tissue and a thin but distinct, internal elastic lamina. The middle layer is almost entirely composed of smooth muscle cells organized in concentric circles. The outermost layer the tunica adventitia, is thick and merges with the surrounding connective tissue. From Wheater et al. (1987).
In Figure 2.10 the various layers of the arteries are shown. Also shown is the size (to order of magnitude) of the various vessels. The walls of arteries larger than about one mm in diameter have their own nutrient blood vessels, the vasa vasorum. These vessels originate either from the parent artery or from a neighboring one and break up into capillary networks, which supply the tunica adventitia and part of the tunica media. The tunica intima and the innermost layers of the tunica media are primarily supplied via transport of materials from the arterial lumen. Due to the complex composition of arterial walls, the distensibility or elastic properties of the arteries are non-linear and therefore not easily described by a mathematical model.

In order to model the mechanical properties of blood flow, an important input parameter to know is the thickness of the arterial wall. It is difficult to describe the wall thickness precisely. The arteries are not loose vessels inserted in the body, they are attached to the surrounding tissue. And the outer layer of the arterial wall, the tunica adventitia, usually merges gradually into the surrounding tissue. We will, however, use the simplifying assumption that the arteries are loose vessels. Generally, the thickness of the arterial wall varies considerably throughout the circulatory system, as is evident from Tables 2.2 and 2.3. Therefore, one often studies the ratio between the wall thickness and the diameter of the vessel. For the larger arteries this ratio is approximately constant, but for smaller arteries it is not constant. Even though the wall thickness decreases as one looks at smaller and smaller arteries, the ratio of wall thickness to radius increases. This increase continues until the smallest of the arterioles, where the external diameter is almost twice that of the lumen, even when the smooth muscle is relaxed. Finally, the thickness of the vessel wall in the capillaries is similar in all mammalian species. This similarity is due to the fact that the wall has to be thin and permeable in order for diffusion of molecules to occur. Capillary walls have a fixed size and structure independent of the species in question. However, it should be noted that the wall thickness of the arteries changes significantly with age, as does the change of the elastic properties of the vessels. Aging causes elastic elements in the wall to degenerate. The vessels may become calcified and the collagen fibers increase in number, replacing muscle-cells and proliferating in other parts of the wall. The overall effect of aging is that the diameter of the vessel increases, and the wall becomes thick and much less distensible.

In Table 2.3 typical values for the various physiological parameters are presented. These are based on measurements from dogs, but the human values for most of the parameters are approximately the same.

2.3.2 Blood

Blood consists of plasma with red blood cells (erythrocytes) white blood cells (leucocytes), and platelets (thrombocytes) in suspension. The primary function of erythrocytes is to transport oxygen and carbon dioxide. Plasma is comprised of 93% water and 3% particles: electrolytes, proteins, gasses, nutrients, hormones, and waste products. Leucocytes are an important part of the immune system. Thrombocytes are a vital component of the blood clotting mechanism, they are not cells, but fragments from plasma cells called megakaryocytes. Erythrocytes comprise more than 99% of all blood cells and approximately 40–45% of the blood (cells plus plasma), this percentage is called the hematocrit. Normally erythrocytes are biconcave discs with a mean diameter of 6–8 $\mu$m and a maximal thickness of 1.9 $\mu$m. The average volume of an erythrocyte cell is approximately 83 ($\mu$m)$^3$ and the number of erythrocytes per mm$^3$ of blood is approximately 5–6$\times$10$^{12}$. Leucocytes, which are roughly spherical, are usually larger than the red blood cells, ranging between 6 and 17 $\mu$m. However their number is small, approximately 7–11$\times$10$^3$ per mm$^3$ in a normal adult. Thrombocytes are much smaller than both erythrocytes and leucocytes. They are rounded or oval and have a mean diameter of approximately 2–3 $\mu$m, so even though there are approximately 2.5$\times$10$^5$ per mm$^3$, their total volume is small. Together leucocytes and thrombocytes have a volume concentration of only approximately one percent of the total blood volume. Furthermore, all these cells are deformable, with the erythrocytes being the most deformable. Significant deformations occur when the cells are passing through the capillaries. However, the cell membranes do not rupture because each cell has a cytoskeleton that supports its shape.

Therefore, the mechanical properties of blood should be studied by analyzing a liquid containing a suspension of flexible particles. A liquid is said to be Newtonian if the coefficient of viscosity is constant at all rates of shear. This condition exists in most homogeneous liquids, including blood plasma (which, since it consists of mostly water, is Newtonian). But the mechanical behavior of a liquid containing a suspension of particles can vary such that the liquid becomes non-Newtonian. These deviations become particularly significant when the particle size becomes appreciably large in comparison to the dimension of the channel in which the fluid is flowing. This situation happens in the micro-circulation (for the small arterioles and capillaries).

Consider a suspension in which the suspending fluid has Newtonian behavior. If the suspended particles are spherical and non-settling, that is, if they have the same density as the suspending fluid, then for any motion the shear stress will be proportional to the rate of shear and the suspension will behave as a Newtonian fluid. This rule applies as long as the concentration of spheres is low, less than 30 percent. This rule was arrived at through experiments performed under steady-
### Table 2.3: Physiological data for the various parameters in the circulatory system (Caro et al., 1978).

**Normal values for canine cardiovascular parameters. An approximate average value, and then the range, is given where possible.**

<table>
<thead>
<tr>
<th>Site</th>
<th>Ascending aorta</th>
<th>Descending aorta</th>
<th>Abdominal aorta</th>
<th>Femoral artery</th>
<th>Carotid artery</th>
<th>Arteriole</th>
<th>Capillary</th>
<th>Venule</th>
<th>Inferior vena cava</th>
<th>Main pulmonary artery</th>
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<td>Internal diameter $d_i$</td>
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<td>$\alpha$ (heart rate 2 Hz)</td>
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<tr>
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Cardiovascular and Pulmonary Physiology and Anatomy

Figure 2.13: The apparent viscosity as a function of the shear rate in human blood. When the shear rate is about 1000 s\(^{-1}\) the non-Newtonian behaviour becomes insignificant, and the apparent viscosity approaches an asymptotic value ranging from 0.03–0.04 g/(cm s) (= 3-4 mN s m\(^{-2}\)). From Caro et al. (1978).

State conditions with suspensions of rigid spheres. These experiments showed that the viscosity of the suspension, defined as the viscosity measured in a particular viscometer under particular conditions, was independent of the shear rate for volume concentrations of suspended spheres up to 30 percent. However, if the suspended particles are not spherical or are deformable in any way, then the shear stress is not proportional to the shear rate, unless the concentration is much less than 30 percent.

The cells suspended in blood are not rigid spheres and the volume fraction of erythrocytes is about 40–45%. Therefore one should expect that the behavior of blood is non-Newtonian. But it has been shown that human blood is Newtonian at all rates of shear for hematocrits up to about 12 percent. In general blood has a higher viscosity than plasma and as the hematocrit is raised, the viscosity of the suspension increases and non-Newtonian behavior is observed, being detectable first at very low rates of shear. Studies with human blood show that viscosity is independent of shear rate when the shear rate is high. With a reduction of shear rate the apparent viscosity increases slowly, until at a shear rate less than 1 s\(^{-1}\) where it rises extremely steeply, see Figure 2.13. The shear stresses can be divided into two groups according to the effect of the shear rate:

- At low shear rates, the apparent viscosity increases markedly. The reason for this increase is that at low shear rates a tangled network of aggregated cell structures (Rouleaux) can be formed. If blood is subjected to shear stress less than a critical value, these aggregated structures form even for standing blood (blood that is not flowing). As a result they exhibit a yield stress. This behavior is, however, only present if the hematocrit is high. If the hematocrit falls below a critical value there are not enough cells to produce the aggregated structures and no yield stresses will be found.

- At high shear rates, the apparent viscosity in small vessels is lower than it is in larger vessels. The progressive diminution with the size of the vessels is detectable in vessels with an internal diameter less than one mm. It is even more pronounced in tubes with a diameter of 100–200 μm. The decreased viscosity with vessel size is known as the Fåhraeus and Lindqvist effect. Experiments were performed at high enough shear rates for the erythrocytes not to aggregate. It was found that the viscosity was approximately constant in vessels larger than 0.1 cm, but when the radius dropped below that, there was a substantial decrease in viscosity. This result is shown in Figure 2.14

In the large vessels it is a reasonable to assume blood has a constant viscosity, because the vessel diameters are large compared with the individual cell diameters, and because shear rates are high enough for viscosity to be independent of them. Hence, in these vessels the non-Newtonian behavior becomes insignificant and blood can be considered to be a Newtonian fluid. Measurements of the apparent viscosity show that it ranges from 0.03–0.04 g/(cm s).
In the micro-circulation, it is no longer possible to think of the blood as a homogeneous fluid; it is essential to treat it as a suspension of red cells in plasma. The reason being that even the largest vessels of the micro-circulation are only approximately 15 cells in diameters. Also, as discussed earlier in this chapter, viscosity starts dominating the mechanical behavior, leading to low Reynolds numbers. Typical Reynolds numbers in 100 µm arteries are about 0.5.

In summary, we can conclude that blood is generally a non-Newtonian fluid, but it is reasonable to regard it as a Newtonian fluid when modeling arteries with diameters larger than 100 µm. For very small vessels it is not easy to reach conclusions as to the Newtonian nature of blood because some effects tend to decrease the viscosity and others tend to increase the viscosity. The latter influence on viscosity is due to a small flow, which increases the viscosity significantly, as well as to the fact that cells often become stuck at constrictions in small vessels. However, cells becoming stuck happens most often in the capillaries. The net effect of all these influences on blood viscosity is that it is reasonable to assume that the overall viscous effects in the small vessels are approximately equivalent to those that occur in the larger vessels.

### 2.4 Cardiovascular Regulation

The regulation of human blood pressure is complex and involves a variety of control mechanisms. The biological function of blood pressure control is to provide adequate blood flow to the various organs connected to the human circulatory system. In essence, pressure control promotes a normal distribution of fluids, hormones, electrolytes and other agents. The regulatory system consists primarily of two types of control mechanisms: a long term control and a short term control. Long term control provides stabilization of blood pressure over longer periods (minutes, hours, and days) whereas short term controls are concerned with the immediate and acute circulatory perturbations (seconds and minutes).

Long term control operates mainly via the renal and hormonal activities. The kidneys increase the output of water and salt in response to an enhanced arterial pressure. These changes in water and salt regulation cause a decrease in blood volume and thus cardiac output. The net effect is a decline in the arterial pressure. A drop in the arterial pressure promotes secretion of renin from the kidneys. The secretion of renin results among other things in formation of the hormone angiotensin II which enhances vessel constriction and thus increases arterial pressure.

Short term regulation is mainly mediated by the central nervous system (CNS) and involves baroreceptors, mechanoreceptors and chemoreceptors. The overall goal of neural control is to redistribute blood flow to the different areas of the body. Nerves communicate the control signals to the heart and the vessels, in response to the needs of the different body regions. Nervous activity in the CNS modifies heart rate, cardiac contractility and the state of vessel constrictions. Chemoreceptors are sensitive to chemicals in the blood and react to alterations in the concentrations of oxygen, carbon dioxide, and hydrogen ions. A drop in arterial pressure may decrease the concentration of oxygen. The chemoreceptors answer by increasing cardiac strength and vessel constriction. Baroreceptors are stretch receptors which are sensitive to pressure alterations. The
most important receptors are located in high pressure regions such as the carotid sinus and the aortic arch. Mechanoreceptors (or low pressure receptors) are located in low pressure areas such as the atrial and pulmonary veins. Mechanoreceptors are also stretch receptors and provide arterial pressure control by resisting alterations in venous volume. Baroreceptors are the best known and easily accessible receptors, consequently they have been investigated extensively. Mechanoreceptors are less studied; quantitative experimental data of these receptors are very sparse (Danielsen, 1998).

The phenomenon of auto-regulation is a local control mechanism independent of the CNS. Local tissues can control blood flow in response to moderate changes in cardiac output and arterial pressure by dilating or constricting vessels. These responses may be due to a contractile response by the smooth muscles when stretched.

### 2.5 Pulmonary Physiology

The main purpose of the respiratory system is to transport oxygen and carbon dioxide between the atmosphere and the tissue and organs in the body. Oxygen is a necessity for life and a human being consumes approximately 260 ml/min at rest (Nunn, 1987). The oxygen is delivered from the atmosphere to the organs and tissue via the lungs and the blood circuit. Carbon dioxide is a waste product of oxidative metabolism, and is carried by the blood in the opposite direction, from the tissue to the lungs, where it is removed by ventilation. The carbon dioxide elimination rate at rest is about 160 ml/min (Nunn, 1987). Since carbon dioxide dissolved in blood forms carbonic acid, which affects the pH value of the blood, the removal of carbon dioxide plays an important role in the acid-base balance in the blood.

The respiratory cycle starts in the atmosphere outside the body, see Figure 2.15. By inspiration oxygen enters the lungs, as 21% by volume of atmospheric air consists of oxygen. During inspiration air enters the lung where it mixes with the air already in the lung. The upper airways and the lungs form a tree structure, i.e. the pulmonary tree, connecting the atmosphere with the alveoli, which are small air-filled sacs. From the alveoli oxygen diffuses across a membrane into the blood of the the pulmonary capillaries, see Section 2.5.2. By this diffusion the content of oxygen in the alveoli is reduced, and hence the expiratory air contains only 16% oxygen.

![Schematic view of the respiratory system](image-url)
2.5 Pulmonary Physiology

Nearly all respiratory gasses are distributed throughout the body by the blood stream. This transport of gasses is much faster than diffusion. Branching of blood vessels into tiny capillaries assures that diffusion lengths are small, both in the lungs and in tissues. Almost all cells in the body are within a few cell diameters of at least one of the smallest branches (Vander, Sherman and Luciano, 1990). When blood flows through the capillaries of the tissues and organs, oxygen leaves the blood stream by diffusion and enters the cells, where it is used for metabolism. Metabolism produces carbon dioxide, which subsequently diffuses into the blood and is carried to the pulmonary capillaries. From here carbon dioxide diffuses over the lung membrane into the alveoli. From the alveoli it is transported through the airways to the atmosphere during expiration.

2.5.1 Ventilation

During normal conditions breathing continuously renews the air in the lungs. During inspiration the air passes from the mouth and nose, through the tree-like conducting airways (Figure 2.16) into the alveoli. At expiration the air flows the opposite way. In the alveoli the air and blood are only separated by a thin membrane through which oxygen and carbon dioxide transfer can take place. The area of the blood-gas membrane of the 3 million alveoli of a standard man is about 90 m² (Grodins and Yamashiro, 1978).

The airways are structured as a binary tree, where each new level of branching, or generation, doubles the number of pipes. The first generation, termed generation 0, consist of a single pipe, named the trachea. The last generation, denoted generation 23, consists of 8 million pipes. The first generations (0–19) are called the conduction zone. Small alveoli sacs appear on the pipes at the later generations (20–23). Consequently these generations are termed the respiratory zone.

The lung and airways have no muscles to drive ventilation. Instead, the lungs function like a bellows, with inflow and outflow driven by forces working solely on the outside. Natural ventilation is similar to the normal operation of a bellows, while artificial respiration by a respirator is similar to filling the bellows by blowing into the pipe.

Natural ventilation is performed by movement of the pulmonary walls generating a pressure difference and thus an airflow between the lungs and the surroundings. The alveoli walls contain a fluid, the interpleural fluid, in the interstitial space between the lung and the thorax, see Figure 2.17. This space constitutes a single connected chamber throughout each lung, and is “fixed”
on the “outside” to the thorax. Consequently forces acting upon any wall of the interstitial space is transmitted by the fluid to all the rest of the walls by a hydraulic principle. Natural breathing results from rhythmic contractions and relaxation of respiratory muscles. At inspiration the movements of these muscles cause the thorax to enlarge. When the thorax is expanded the force is transmitted to the lung via the interpleural fluid, forcing each alveolus to enlarge. The expansion causes the pressure within the alveoli to drop to less than atmospheric and the pressure difference causes an air flow into the alveoli. The ability of the lung to expand is termed elastance and the inverse of elastance is called compliance.

Pressure from the interstitial space gives the lung an elastic recoil. Normally expiration is caused only by this elastic recoil driving the air in the lungs the opposite way, but active forces contracting the thoracic cage can be applied. At the end of an expiration the interstitial space has a pressure slightly below atmospheric pressure. The force from the interpleural fluid thus prevents collapse of the alveoli.

During artificial ventilation the driving forces of the respiration muscles are replaced by an externally driven pressure source such as a respirator. Inspiration is obtained by raising the pressure in the ventilatory mask, and thus forcing air into the lung. When the pressure is removed elastic recoil drives expiration.

The volume of air flowing into and out of the lungs during each breath is called the tidal volume, see Figure 2.18. The tidal volume is about 0.5 l at rest. A small amount of air, approximately 0.15 l, only reaches the conducting airways, and will be expired without any exchange with the blood. This amount is called the anatomical dead space. Thus, approximately 0.35 l per breath participates in gas exchange. At a breathing rate of 15 breath per minute this gives a volume flow rate of 5.25 l/min.

Ventilation disorders are normally split into two types, obstructive and restrictive, respectively. In obstructive ventilation disorders the flow of air through the airways is obstructed. Restrictive disorders are cases in which regions of the lungs are damaged, resulting in lower compliance and possible decreased permeability of the lung membrane.

2.5.2 Gas Exchange Between Lungs and Blood

When the inspired air reaches the alveoli there is only a thin permeable membrane of 0.2 \( \mu m \) separating the air from the blood in the approximately 1800 capillary vessels surrounding each alveolus (see Figure 2.19). Consequently, \( O_2 \) and \( CO_2 \) are rapidly exchanged (Grodins and Yamashiro, 1978).

Oxygen and carbon dioxide move between the alveoli and blood by simple diffusion. The mechanism of diffusion between air and blood may be understood by considering a small container, half filled with water. The random thermal motions of the gas molecules will let the gas diffuse to areas where the pressure is low, even into the liquid. Since diffusion happens by random movements, a larger number of molecules in one region will result in more molecules diffusing out of that region. Eventually the random movements of molecules from the gas phase to the liquid phase will equal the random movements in the opposite direction and thus an equilibrium state is reached. At equilibrium the pressure of the gas is uniform throughout the container.

The relationship between the concentration of a gas dissolved in a liquid and the partial pressure expresses the distribution of gas between the two phases. If no chemical reaction takes place the concentration in the solvent is, to a good approximation, proportional to the pressure. The proportionality factor expresses the solubility of the gas in the liquid. A highly soluble gas will come to an equilibrium with a large number of molecules per volume of the liquid, while a gas with a low solubility will have more gas molecules in the gas phase, see Figure 2.20. The solution of a gas in a liquid may include effects other than
Figure 2.18: Lung volumes during the breathing cycle. The tidal volume in the normal respiration, but both expiration and inspiration can be increased, yielding the vital capacity.

Figure 2.19: An alveolus and a capillary. Each alveolus is typically surrounded by 1800 capillaries.

random thermal movements, as some gas molecules may react with molecules in the liquid. Yet, regardless of how the gas dissociates in the liquid, the gas will adjust towards equal partial pressure in liquid phase and gas phase.

In order to distinguish between gas in the gas phase and gas dissolved in liquid, we use the term pressure for gas in the gas phase and the term tension for the pressure of the gas dissolved in liquid.

Oxygen is poorly soluble in water. Consequently, the high concentration of oxygen in blood is due to its chemical binding to components in the blood. Without these oxygen carrying components a very high partial pressure of oxygen in the alveoli or
a much faster blood flow would have been required, in order to transport the needed 260 ml of oxygen each minute. At normal atmospheric pressure and with the normal amount of blood components more than 98% of oxygen in the blood is bound to components in the blood.

The main carrier of oxygen in the blood is hemoglobin, a protein found in erythrocytes (red blood cells), see Section 2.3.2. Oxygen is reversibly bound with hemoglobin. Hemoglobin combined with oxygen is denoted oxyhemoglobin, while hemoglobin not combined with oxygen is termed deoxyhemoglobin or reduced hemoglobin. Carbon dioxide is much more soluble in blood than oxygen is, but its transport is also improved by chemical reactions. Dissolved carbon dioxide reacts reversibly with water and with hemoglobin. Consequently some carbon dioxide is transported as bicarbonate or carbamino compounds.

When carbon dioxide reacts with water an acid is formed, and hence there is a close relation between the carbon dioxide level and the acid-base balance in blood. The acid-base balance is expressed by the pH value, which is the negative logarithm of the concentration of hydrogen ions. Fluctuations in the pH value are buffered by the way hydrogen ions participate in certain chemical reactions in blood. Hydrogen ions combine with bicarbonate ions and hemoglobin, and therefore the pH value influences the dissociation of both oxygen and carbon dioxide in blood.

Even in this complicated interaction, in which the two gases affect the dissociation of each other through chemical reactions, the gases will each reach an equal pressure between the blood and the surrounding tissue or alveoli, as long as the membrane separating the two phases is permeable. This happens because the equilibria of the chemical reactions are shifted, when soluted gas diffuses across the membrane.

In cases of respiratory disorders or hard work, the oxygen supply might become insufficient. In such cases metabolism occurs in absence of oxygen. However, carbon dioxide is also a waste product of this anaerobic metabolism, and is still removed from the tissues by blood. If the elimination of carbon dioxide through the lung is reduced the consequence will soon be an increased amount of carbon dioxide, and hence a decreased pH value, in the blood.

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