Pressure Oscillation in Biomedical Diagnostics and Therapy

Ahmed Al-Jumaily, Lulu Wang

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In the name of the CREATOR who fashioned humankind as the best of his creations.
To my wife Thana who stands by me in light and dark times.
To my kids, candles of my life.
To my postgraduate students from whom I have humbly learnt.

Contents

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Ahmed M. Al-Jumaily is currently a Professor of Biomechanical Engineering and the Founder of the Institute of Biomedical Technologies at the Auckland University of Technology, Auckland, New Zealand. He holds a PhD and MSc from the Ohio State University, USA, and a BSc from the University of Baghdad, Iraq. He is a Fellow member of the American Society of Mechanical Engineers (ASME) and the Acoustical Society of America in addition, to being a member of 11 more international professional societies. He is the Editor-in-Chief of the ASME Journal of Engineering and Science in Medical Diagnostics and Therapy, the Editor for the ASME monograph series-Biomedical and Nanomedical Technologies, and has been on the editorial and refereeing boards for several international journals. He has published more than 360 papers in international journals and conference proceedings including two ASME books on Vibration and Acoustics in Biomedical Applications and a third one on CPAP devices. He has supervised more than 100 postgraduate students from 35 countries in biomedical applications, vibrations, biomechanics, and electroactive polymers. During his academic career, he has forged strong alliances between academia and industries, in particular, in the medical devices area, which has resulted in many successful grants and contracts with companies and research organizations. Al-Jumaily's current research focuses on biomedical applications, particular interest in the applications of vibration and acoustics to airways constriction therapies, and artery noninvasive diagnostics.

Lulu Wang is currently a Distinguished Professor of Biomedical Device Innovation Center at Shenzhen Technology University in China. She received the ME (First class Hons.) and PhD degrees from the Auckland University of Technology, New Zealand, in 2009 and 2013, respectively. From 2013 to 2015, she was a Research Fellow with the Institute of Biomedical Technologies, Auckland University of Technology, New Zealand. In June 2015, Dr. Wang became an Associate Professor of biomedical engineering with the Hefei University of Technology. In June 2019, she became a Distinguished Professor of Biomedical Engineering at Shenzhen Technology University. Her research interests include medical devices, electromagnetic sensing and imaging, and computational mechanics. Over the past 5 years, Dr. Wang has authored more than 70 peer-reviewed publications, 2 ASME books, 7 book chapters, and 10 issued patents. Dr. Wang is a member of ASME, IEEE, MRSNZ, AAAS, PSNZ, and IPENZ. She is an active reviewer of numerous journals, books, and conferences. She has edited four books and three special issues of international journals. She has received multiple National and International Awards from various professional societies and organizations. She is an active organizer of several international conferences include ASME, IMECE, and ICCES.

Preface

This book compiles over 20 years of research and development in applying physiology and engineering principles to designing, modeling, and improving diagnostic and therapy devices and methods to serve the medical community. The fundamental and frontier theories and techniques of low- and high-frequency pressure oscillation are presented as the foundation for these principles. This area is evolving very fast, and documentation of such schemes is essential for various industries and clinical applications. Currently, there is no book with this title available in the open literature.

The book consists of eight chapters. Each chapter has a stand-alone content starting with an introductory material on the subject matter, followed by a review of available technologies to diagnose or treat the diseases with intensive literature survey, and then introducing the significance of pressure oscillation in the diagnostic or therapeutical applications. Each chapter finishes with some clinical applications and voluminous references and bibliography.

The first chapter is an introductory chapter which presents the foundation materials for the rest of the book. It introduces the basic principles of pressure oscillation and how they can be formulated into mathematical equations. The chapter explains how these equations can be converted to practical applications for biomedical diagnostics or therapy. The book is then split into two parts as detailed below.

Part I of the book consists of three chapters focusing on diagnostics, imaging, and characterization. Chapter 2 presents an application of pressure oscillation to develop a diagnostic technique. It briefly describes the basic concepts of arteries, arterial stiffness, arterial blood pressure, and pulse wave. It reviews several methods for measuring these variables. Various new contributions are discussed, including physics-based waveform measurements and human systemic arterial numerical models. Several medical applications of pulse wave analysis are also presented. The basic principles of converting pressure oscillation to a tool in biomedical imaging will be clearly explained in Chapter 3. Two of the methods will be explained in detail: (i) radiation force (RF), which is normally generated by high-frequency pressure oscillation. Several new radiation force-based elasticity imaging (EI) methods were proposed in the past two decades, and these techniques generate radiation force to an object and measure its dynamic displacement response in order to estimate the object's mechanical properties. (ii) Vibro-acoustography (VA) is a speckle-free acoustic radiation force (ARF)-based EI technique, which can visualize healthy and abnormal soft tissue through mapping the acoustic response of the object to a harmonic RF induced by ultrasound. This chapter briefly describes the history of ARF and its applications and provides an overview of ARF-based EI approaches. Examples of ARF-based EI–VA imaging and multifrequency VA techniques and their applications in medical and material evaluation areas are discussed. Several advantages and disadvantages of VA, comparison between VA and pulse–echo systems, as well as future directions are presented.

Respiratory diagnostic and characterization technique are summarized in Chapter 4. The forced oscillation technique (FOT) is a low-frequency-pressure wave technique. It has been used in the measurement of respiratory impedance and has evolved into powerful tools for the assessment of various mechanical phenomena in the mammalian healthy and diseased lung. This chapter briefly reviews the human respiratory system (RS) and its functions, mechanics, and various developed models and measurement methods. An example of the RS measurement method FOT is detailed, including working principles, instrumentation, measurements arrangement, and impedance measurement methods. Finally, clinical applications of FOT are also described.

Part II of the book focuses on respiratory therapies. To be equipped with sufficient knowledge on lung ailments in the upper, central, and lower airways covered in this section, an introductory chapter on the respiratory system is needed. Chapter 5 presents lung mechanics, how each part of the lung is associated with various diseases, and how pressure oscillation can target these parts and help in treating these diseases. In Part II, the following three chapters deal with specific diseases, namely, obstructive sleep apnea (OSA), asthma and respiratory distress syndromes (RDSs).

Chapter 6 briefly describes OSA syndromes, diagnostic methods based on the combined evaluation of clinical manifestations and objective sleep study findings, and currently available treatment methods. Polysomnography represents the gold standard to confirm the clinical suspicion of OSA syndrome, to assess its severity and to guide therapeutic choices. Continuous positive airway pressure (CPAP) is currently the most recommended method for OSA treatments. Some basic working principles of CPAP techniques and their types are discussed. Finally, clinical applications of these devices for the treatment of OSA and benefits are also highlighted. A new technique is introduced and detailed on how pressure oscillation can be used to improve the use of CPAP.

The importance of airway smooth muscle (ASM) in asthma was realized almost 150 years ago. Breathing has a strong relaxing and protective effect on ASM, inhibiting airway constriction. Understanding the behavior of ASM is crucial to understanding the reversible airway obstruction central to asthma. Chapter 7 briefly describes the basic concepts of asthma, ASM, and dynamic behavior of ASM through both experimental data and modeling results. A fading memory model is given to further describe the behavior of contracted ASM for finite duration length steps and longitudinal sinusoidal oscillations. Finally, the potential of pressure waves superimposed on breathing patterns in treating asthma is investigated using experimental research and animal models.

Chapter 8 briefly introduces the common neonatal respiratory diseases with traditional surfactant therapies and respiratory support devices currently used in practice. Various pressure oscillation techniques including high-frequency ventilation (HFV), continuous positive airway pressure (CPAP), and “noisy” ventilation as effective and cheaper methods for respiratory support are discussed. Clinical trials that describe the effectiveness of using such treatments are presented. The concept of stochastic resonance and its application to "noisy" ventilation are introduced. The potential advances in the use of pressure oscillations and "noisy" ventilation to treat both neonatal and adult diseases are presented.

This book can teach students how to turn mathematical equations into medical devices or methodologies, and it also offers an excellent reference for undergraduate and postgraduate students in Physiology, Radiology, Applied Mathematics, Physics, and Biomedical, Mechanical, and Electrical Engineering. The book will also appeal to fellow researchers, practitioners, lecturers, and professionals such as Biomedical Engineers, Clinicians, Medical Doctors, Radiologists, and Researchers in Biomedical Imaging, Diagnostics and Therapies, and medical device industry personnel. It is a helpful compilation that familiarizes the reader with practical modeling approaches to enhance the design process.

Introduction

The primary objectives of this book are to present recent developments, discoveries, and progress made in the implementation of pressure waves in biomedical diagnostics and therapies, with a focus on the arterial and respiratory systems. Based on engineering principles and physiology, the fundamental and frontier theories and techniques of low- and high-frequency pressure waves are applied to develop medical devices and technologies for biological systems imaging, diagnostics, and therapies. It is an interdisciplinary area which utilizes Mathematics, Physics, Chemistry, Engineering, Computer Sciences, Physiology, and other fields for Clinical Applications. As biomedical technologies are evolving very fast, documenting of such schemes are essential for medical industries and clinical applications.

The book is compiled of learning and findings gained in more than 20 years of research and development that I have conducted with my postgraduate students at the Auckland University of Technology. Each chapter summarizes a complete project, which is further detailed in theses cited as references. In this way, I would like to acknowledge the contributions of all my postgraduate students whose works are used as the main reference material for this book. I would also like to acknowledge my appreciation to other authors in the field, whose contributions are evidenced in the voluminous references and bibliography. Further, I would also like to acknowledge the effort of my previous student and postdoc, and current colleague, co-author Dr. Lulu Wang who has helped to compile some of the materials from my team's work during her postdoc position. Final reading of the manuscripts by Yelena Dumanovic is much appreciated.

1

Pressure Waves for Diagnostics and Therapy

1.1 Introduction

To understand the role of mathematics in an engineering discipline, we may talk about the capability of an engineer. Inspired by the laws of physics, an engineer uses mathematics as a tool to convert nature's resources to a product. This definition may be considered out of date now. A better definition may take the form: inspired by the laws of physics, using mathematics as a translator, to convert nature's resources to a product or to study a phenomenon (or phenomena) or a criterion (criteria). This latter definition takes engineers to go far into space and deep into the human body microstructure in order to investigate, analyze, and apply this knowledge to innovations for the betterment of the humankind. The process modeling could be done in the form of mathematical modeling or/and computer simulation.

1.2 Significance of Biological System Modeling

Various physical and biological systems can be modeled in the form of mathematical equations. The question often raised is why we put so much emphasis on mathematical modeling? The answer to this is the fact that mathematical modeling has so many advantages including but are not limited to:

1) It is a tool that helps to convert basic laws of nature (physics, chemistry, biology, etc.) to industrial application.
2) It converts real systems of interest into models which can be analyzed and tested on a piece of paper or a screen.
3) Nowadays, computers and new technologies have made math the most valuable tool to convert complicated real-life system into a virtual environment on the screen.

Of course, talking about math here implies all types of mathematical approaches including but not limited to differential mathematics, computational, statistical, and others. Statistical models applied to experimental data, as an example, may help in understanding the results for the purpose of assurance or development of a useful future formulation.

The two "Engineering" definitions stated earlier may sound the same; however, the second one is more general, and it represents the current methodology for engineering research. No more the engineer only designs and develops. Engineers go beyond the scope

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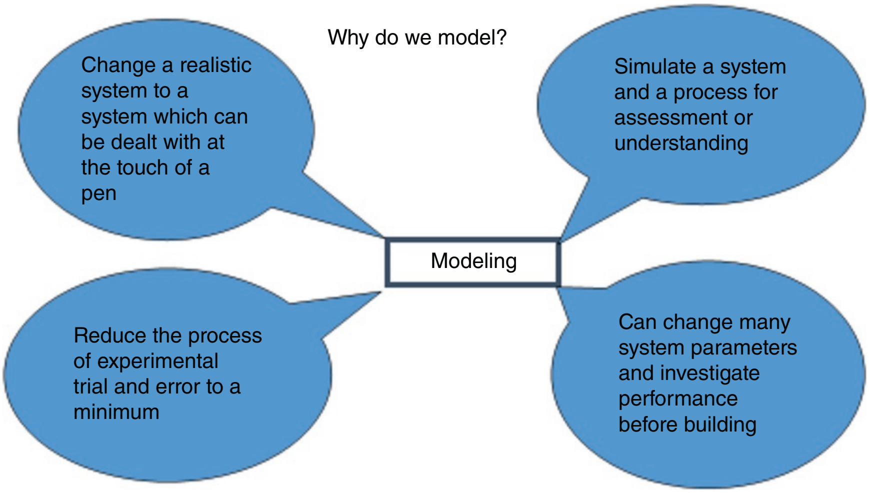

Figure 1.1 Advantages of mathematical modeling.

of developing a product to help humankind, by studying and investigating various systems and behaviors whether natural or synthetic. A biomedical engineer is not only responsible to build a medical device, a biomedical tool, or an artificial body part. Many biomedical engineers focus on investigating biological behaviors or responses in an optimum goal of serving the human body needs. Thus, this aligns with the second definition of "Engineers" stated earlier. The question which is normally raised is "what do we do with this modeling?" The response to this is summarized in Figure 1.1. While changing a realistic system, whether extremely large or at a nanoscale, to a system which can be represented virtually on a screen and reducing the process of experimental trial and error to a minimum time and cost without jeopardizing integrity are typical processes of mathematical modeling. Modeling could be used to simulate a system or a process to understand and assess, to change system parameters, and to investigate performance before building the device while reducing the time and costs of experimental investigations of the complicated very large or very small systems to investigate them. With this in mind, the main outcomes of the modeling process are

1) To turn unreachable systems to accessible ones.
2) To allow studying the real system without affecting or damaging it.
3) To keep a system model ready on the screen to optimize, design, analyze, etc.
4) To change the parameters and see how the system behaves.
5) To create specifications for the system to be ready for manufacturing.

Accessing unreachable systems and converting them to reachable has a very wide range of applications, particularly in the biomedical field. A study of an organ or a cell behavior is difficult if not impossible within the living human body. Thus, having a model on the screen helps to introduce many variations without affecting the human body as a living system itself. Further, if a model for a device to support the human body such as an artificial kidney is developed and needs optimization. A mathematical model for this device is extremely helpful in the process of designing and optimizing without jeopardizing the health of the person. Multiple variations of parameters and its effects could be studied affecting the human body itself. Obviously, out of the last design iteration and optimization process, new specifications could be generated for optimal operation and performance. However, the question which is always raised is how reliable modeling is? The answer is summarized by the following facts:

- Pace of technological change drives industries to implement modeling.
- Aircraft, underwater, space, and other industries have produced good and reliable models for the development of their products.
- Most research groups have developed reliable models in their fields of research and have worked with confidence to move toward innovation.
- Experience plays an important role in reliability.
- If a model is not perfect, its value at least is to show the trend of the behavior or variations.

Over the years and with the development of the computational capabilities, mathematical modeling has demonstrated advancement and success in all modern technologies, from space engineering to nano cells within the human body. All systems generated from modeling have worked reliably and with improved performance. Of course, like any other discipline, experience plays an important role in developing the best model for a particular device or a process. In general, if the model is not perfect, it will show the general trend of variation for the process or operation.

Without going into details of modeling, in this chapter, we will focus on the development of a single equation, as an example of modeling of one of the biological systems such as the respiratory or cardiovascular system and for the purpose of developing a medical diagnostic tool or therapy device/method or to investigate the behavior and measure performance. This simple equation is the wave equation. The nature of several systems within the human body conveys fluid for the purpose of living, particularly, the cardiovascular and the respiratory systems. In spite of the large differences between the functions of these two systems, wave propagation through them can be tuned into a diagnostic or a therapy approach. The significance of this equation will be clarified in Chapters 2, 3 and 5, but at this stage we will derive the equation and outline its significance for biomedical diagnostics and therapies.

1.3 Wave Equation

In this book, we focus on how mathematics can be applied as a modeling tool to convert basic laws of physics, biology, and chemistry sciences to a process, protocol, method, or/and a medical device, which can deliver an outcome for diagnostics or treatment for some critical lung, heart, or arterial diseases. Our focus will be on the simple wave equation, its basic principle, application, and how it can be used to investigate various biological processes and how this powerful equation could be used to develop a medical device for diagnostic purposes as well as various tools for treatments. There are many ways of deriving this equation from a simple string to a rod (bar) and to the flow in pipes. In this chapter, we focus on equations defining the flow in the pipes as it resembles an artery or an airway passage in the context of the human body.

Various transmission lines in the respiratory and cardiovascular systems may be treated as branching compliant tubes conveying fluid. Blood flow in the arterial system and airflow in the respiratory system induce forces and stresses in the arterial and respiratory walls, due to complex fluid–structure interactions. These forces and stresses play an important role in the onset and progression of many acquired and congenital cardiovascular diseases, such as arterial atherosclerosis and aneurysms, and airway ailments such as obstruction in obstructive sleep apnea and narrowing in asthma.

The blood flow in the arterial system and the airflow in the respiratory system diseases have a common physical problem which is change in the fluid flow passage as "restriction" or "enlargement" of fluid flow passage. Atherosclerosis, for example, involves the accumulation of plaque in the *intima* of the arterial wall, which reduces arterial lumen and increases local arterial stiffness. There is substantial evidence on the localization of these plaque deposits at sites with hemodynamic conditions commonly characterized by low wall shear stress (Caro et al. 1971; Taylor 1959). Aneurysms, on the other hand, involve the degradation of local arterial wall tissues, resulting in lowering of local arterial stiffness and enlargement of local vessel cross section. If, in extreme cases, the wall stress due to the transient fluid–structure interactions exceeds the strength limit of the dilated artery wall, it causes vessel rupture leading to death from internal hemorrhage which has been reported to be between 80 and 90% of the cases (Scotti et al. 2005). Aneurysms are common in locations with secondary flow and flow recirculation even in normal resting conditions (Peattie et al. 2004; Lasheras 2007).

In the respiratory system, on the other hand, the change in the air passages is due to either an "obstruction" or a "narrowing." The former is typical in obstructive sleep apnea where the upper airway tissue loses their capability to respond and may collapse and introduce obstruction. However, in asthma, the airway smooth muscles are considered as the main mechanism to introduce airway narrowing by a physiological process called cross-bridge cycling.

Considering the correlations between the various hemodynamic and aerodynamic conditions, and the onset and progression of different cardiovascular and respiratory diseases, there is worldwide consensus on the need for enhancements in the current understanding of cardiovascular mechanopathobiology (O'Rourke and Hashimoto 2007) and respiratory airflow dynamics. Since blood flow, airflow, and pressure are dependent on several factors in addition to physical phenomena, experimental studies demand rigorous screening, which make them expensive and time-consuming. A preferred mode of investigation is by computer simulation using mathematical models which in principle are based on the wave equation.

Principles of conservation of mass, momentum, and energy form the theoretical bases of mathematical models that have been developed for the study of the physical aspects of blood flow and airflow. However, an analytical solution of the full form of these equations has not been developed where only solutions for special cases are available today. Proper application of numerical techniques for solving these equations demands familiarity with assumptions and approximations that can be made to achieve a reasonable solution. This chapter develops a mathematical model capable of representing pressure propagation in human blood and respiratory air passages and use of this model to investigate the significance of different physical terms within this model on pressure propagation in any of the passages.

Although the development of one-dimensional mathematical models for studying pressure propagation in biological cylindrical tube-type passages and the effects of some phenomena have been previously discussed in the literature (Reuderink et al. 1989; Sherwin et al. 2001; Nardinocchi et al. 2005), the same equation can be derived for a wave traveling in a medium which could be used in the diagnostic process for cancer detection; see Chapter 3. Further, previous publications assume the special approximation to these passages such as to be straight and either linearly or exponentially tapered which is not anatomically representative. In this chapter, the general form of the wave equation is derived and discussed for the purpose of simplifying the process to develop a diagnostic or therapy device, method, or protocol.

The general form of deriving the governing equations for the wave propagation in a compliant tube conveying fluid leads to the partial differential equations which have a complex mathematical involvement without important physical significance. Therefore, a number of assumptions are made and justified to produce a practical model for the wave propagation.

In this chapter, it is assumed that the fluid conveyed by the tube is homogenous and nonviscous. This is obviously not true as the blood is both nonhomogenous and viscous. However, work by Taylor has shown that the effects of nonhomogeneity and viscosity of the fluid are only significant in tubes with very small diameters such as arterioles (Taylor 1959). In addition, it is assumed that the tubes are of cylindrical shape and elastic. The tube walls are nonlinearly viscoelastic, but work by Fung (1997) showed that the effect of nonlinear viscoelasticity on wave propagation is not important.

1.4 Governing Equation

The two main reasons we are focusing on the wave equation in this introductory chapter are as follows:

1) The main elements considered in this book are compliant tubes to represent the arterial and the respiratory system passages. Both the diagnostic and therapy techniques developed in this book can be easily explained by using the one-dimensional wave equation.
2) Although this equation will be used mainly for the two systems stated earlier, the equation could be used to explain the transmission and reflection of waves in any medium.

1.4.1 Assumptions

To derive this equation and to avoid nonlinear complexity, the following assumptions are made:

1) It is assumed that the length of the tube is long compared to its diameter. This assumption surely holds for passages in the conductive airways as well as for the central systemic arteries; thus, it can be hypothesized that the flow is one-dimensional (Lasheras 2007).
2) No friction, work, or heat transfer.
3) No action at a distance force.
4) Constant area except for radial elastic deflection.
5) Assume the density ρ of the conveyed fluid, blood or air, is constant.
6) The tube wall Young's modulus of elasticity E is assumed constant.

7) It is also assumed that the tube is thin-walled and obeys Hooke's law. Hence, any small change in transmural pressure dp is balanced by a change in the tube circumferential tension.

1.4.2 Derivation

By considering the free body diagram shown in Figure 1.2, the basic equations of conservation of mass and momentum can be derived by considering mass conservation in the segment of a passage dx as shown in Figure 1.2a which leads to

$$\frac{\partial A}{\partial t} + \frac{\partial}{\partial x}(Au) = 0 \tag{1.1}$$

Balancing the forces acting in the axial direction on a fluid element dx and cross-sectional area A as shown in Figure 1.2b leads to,

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} + \frac{1}{\rho}\frac{\partial p}{\partial x} = 0 \tag{1.2}$$

where u is the velocity of the fluid.

Considering assumption 5 and 6 and from equilibrium of the forces acting on a free body shown in Figure 1.3, one can write that the stress–strain relation can be written as:

$$\frac{Ehdr}{r} = rdp \tag{1.3}$$

Equations (1.1)–(1.3) can now be used to derive an equation governing steady-state flow through an elastic artery, and with further simplifications the theoretical artery wave speed can be determined.

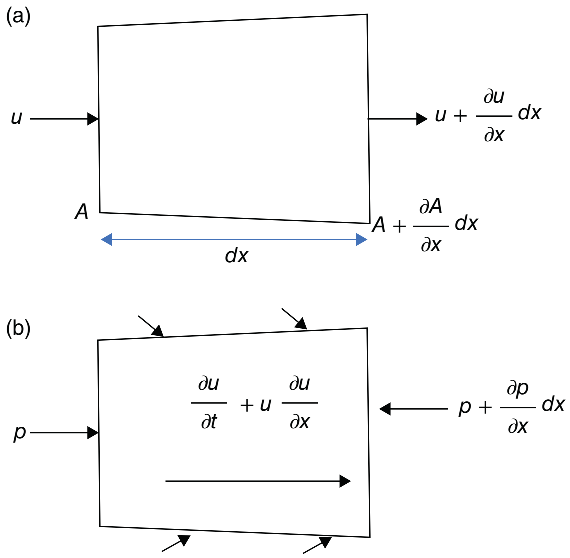

Figure 1.2 Free body diagram of a tube segment showing mass (a) and momentum (b) conservation.

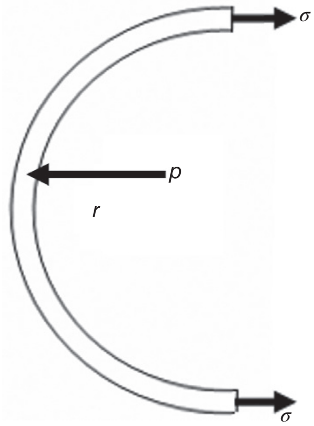

Figure 1.3 Forces equilibrium tube segment free body diagram.

Equation (1.1) is linearized by substituting $A = \pi r^2$ and by assuming that the wave amplitude is much smaller than the wavelength. Neglecting the second-order terms reduces the equation to:

$$\frac{\partial u}{\partial x} + \frac{2}{r}\frac{\partial r}{\partial t} = 0 \tag{1.4}$$

Equation (1.2) can also be linearized by taking into account small disturbances in a motionless tube filled with fluid. Hence, the $u\frac{du}{dx}$ term is not significant and equation (1.2) can be written as:

$$\frac{\partial u}{\partial t} + \frac{1}{p}\frac{\partial p}{\partial x} = 0 \tag{1.5}$$

Combining equations (1.3) and (1.5) results in:

$$\frac{\partial u}{\partial x} + \frac{2r}{Eh}\frac{\partial p}{dt} = 0 \tag{1.6}$$

Differentiating equation (1.4) with respect to x and equation (1.6) with respect to t, then neglecting the second-order terms and substituting gives

$$\frac{\partial^2 p}{\partial x^2} + \frac{1}{c^2}\frac{\partial^2 p}{\partial t^2} = 0 \tag{1.7}$$

where

$$c^2 = \frac{Eh}{2\rho r} \tag{1.8}$$

1.4.3 Solution

Equation (1.7) is the wave equation which governs the pressure wave, Figure 1.3, where c is the wave speed:

$$c = \sqrt{\frac{Eh}{2\rho r}} \tag{1.9}$$

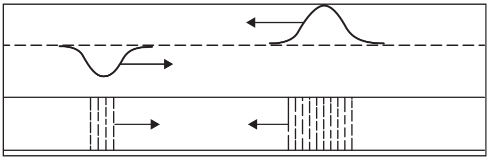

Figure 1.4 Pressure traveling waves: compressed and expanded.

The speed of sound c is a function of three main variables which significantly affect the traveling wave:

1) Geometry, namely, h and r.
2) material properties, and
3) fluid density.

If any of these properties changes, it will reflect on the shape of the traveling wave. This will influence the wavelength, frequency, and the shape of the wave, Figure 1.4, which may be implemented in a diagnostic procedure. However, we may use the pressure to forcibly change those parameters which can be implemented in a therapy scenario. These two scenarios can be used to develop a diagnostic device/method or a therapy device/method. Based on this fact, this is a powerful equation which could be used for diagnostics and/or therapy in many biomedical applications. The main parameter c plays an important role in the application. Clearly, it is a function of the tube wall properties E, h, and r and the fluid density ρ.

The solution of equation (1.7) can be written as:

$$P(x,t) = P_0 f(x - ct) + P'_0 f(x + ct) \tag{1.10}$$

where $P_0 f(x - ct)$ represents an incident pressure wave traveling in the positive x direction and $P'_0 f(x + ct)$ represents a pressure wave traveling in the negative x direction. Those traveling waves can reflect at any point due to a change in any of the properties. At any section along the length, if h, r, E, or ρ changes the wave will split into two, where one will travel through as an incident wave $P_0 f(x - ct)$ and the other $P'_0 f(x + ct)$ will reflect back as a reflected wave. The values of these waves depend on the transmission and reflection parameters explained later in this chapter. Thus, at any section, the net wave will be the superposition of the two.

1.5 Bifurcation

Pressure waves are partially reflected when they experience a sudden change in the medium of transmission such as a bifurcation, change in the properties, or a sudden change in the arteries or respiratory airway's geometry or material properties. Central arteries such as the aorta bifurcate into a number of smaller arteries and in some diseases such as aneurysms where discrete batches of the arteries degenerate and hence there is a large change in