Mathematical modelling of the cardiovascular system

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Abstract. This paper is an introduction to the special issue of the Journal of Engineering Mathematic (Volume 47/3–4, 2003) on the mathematical modelling of the cardiovascular system. This issue includes the *2003 James Lighthill Memorial Paper* written by Pedley [1] on the mathematical modelling of arterial fluid dynamics. This introduction is written to bring cardiovascular biomechanics to readers with a background in mathematical modelling and computational mechanics. The importance of mathematical modelling for physiological understanding, diagnostics, prosthesis development, patient selection and medical planning is indicated and discussed shortly. A subdivision into models for cardiac mechanics, pressure- and flow-wave propagation, mass transfer and fully three-dimensional fluid-structure interaction is made and references are given to the different contributions of the issue.

Key words: arterial fluid dynamics, arterial pressure and flow waves, arterial wall mass-transfer, cardiovascular biomechanics, cardiovascular fluid-structure interaction, cardiac mechanics, model based diagnostics and medical planning

1. Introduction

1.1. Mathematical modelling

Mathematical modelling has become an important aspect of physics from the moment Isaac Newton published his *Mathematical Principles of Natural Philosophy*. His scientific way of analysis using mathematical models to describe theory based on experimental evidence has found its counterpart in many disciplines of science ever since. In medical science, however, due to the physical complexity and difficult experimental accessibility of biological systems, mathematical modelling has not enjoyed a comparable interest. Consequently, medical treatment at present is still mainly based on consensus about the behavior of the human body and rarely supported by predictive modelling. Progress in analytical and computational mathematics, better understanding of living systems, and new techniques, like magnetic resonance, in modern medical imaging, however, have led to new prospects of improved medical health care in which mathematical modelling becomes increasingly important and will predict behavior of the human body as a response to internal or external changes.

1.2. Cardiovascular biomechanics

Biomechanics is one of the disciplines related to medical science in which the role of mathematical modelling is evident. Fung [2], one of the founders of modern biomechanics, defined biomechanics as the mechanics applied to biology: the research discipline that studies the mechanical properties of organisms and helps in understanding of their normal and patholo-

gical function, helps to predict their adaptation to changing circumstances and helps in finding methods for artificial intervention.

Cardiovascular biomechanics is that part of biomechanics that focuses on the cardiovascular system: the heart and blood vessels. It comprises the study of the functioning of the heart muscle and its valves, the mechanics of blood flow and wall motion in the heart and blood vessels and the exchange of nutrients and oxygen with waste products and carbon dioxide in the tissues of the organs. Moreover, cardiovascular biomechanics comprises the study of mechanical factors that are of importance for cardiovascular diagnostics, therapy selection, surgery and interventions. It is a research area where solid and fluid mechanics meet and in which both the solid (vessel wall, heart valve and heart muscle) and the fluid (blood) have a complex nature and are dynamic in structure and property.

2. The cardiovascular system

2.1. Anatomy and patho-physiology

For an extended description of cardiovascular anatomy and physiology, the reader is referred to textbooks like the *Textbook of Medical Physiology* by Guyton and Hall [3, pp. 107–293] or the book of Berne and Levy [4]. A biomechanical view to the cardiovascular system can be found in the book *Biodynamics: Circulation* of Fung [5]. Here we confine ourself to the schematic representation given in Figure 1. In this figure it is indicated that from a mechanical point of view, the cardiovascular system consists of a heart acting as a four-chambered pump that propels blood around the circulatory system. Cardiac impulse transmission of the depolarization wave determines the contraction of the heart muscle while the valves between the atria and ventricles, respectively, the ventricles and the main arteries take care of unidirectional blood flow. The systemic circulation consists of an arterial system branching in many arteries of decreasing diameter, a capillary micro-circulatory system in the tissues and a venous system with venules and veins merging into larger vessels transporting blood back to the heart. A close look at the physiological functioning of the cardiovascular system learns that it is highly optimized and self-regulatory under the condition that all parts function properly.

In the western world, however, the rate of mortality originating from cardiovascular disease is more than 40%. In addition to congenital diseases of the heart, its valves or the large arteries, atherosclerosis is the most important pathology of the cardiovascular system and the major cause of cardiovascular disease. Atherosclerosis reveals itself in a progressive narrowing of the arteries as a result of deposition of fat and smooth muscle cells in the artery wall: the development of atherosclerotic plaques. This may lead to partial or fully occlusion of the vessel or occlusion of smaller distal vessels caused by embolism. This can result in insufficient blood supply to the distal tissue (ischemia). Unfortunately this process is often found in sites that are essential for normal functioning of the human body like the coronary arteries, (myocard infarction), the arteries of the brain (stroke) and the peripheral arteries in the legs (claudicatio). Smoking, hypertension, increased cholesterol level are frequently mentioned, but these are certainly not all the factors that are of importance for the development of atherosclerosis (atherogenesis). Of all these factors, the underlying mechanisms that results in atherosclerosis are not yet, or only partly, known. Atherosclerosis is found at specific sites of the arterial system often near bends and bifurcations (see for instance Giddens *et al.* [6]). This indicates that hemodynamic factors like wall shear stress and particle residence time play a role in

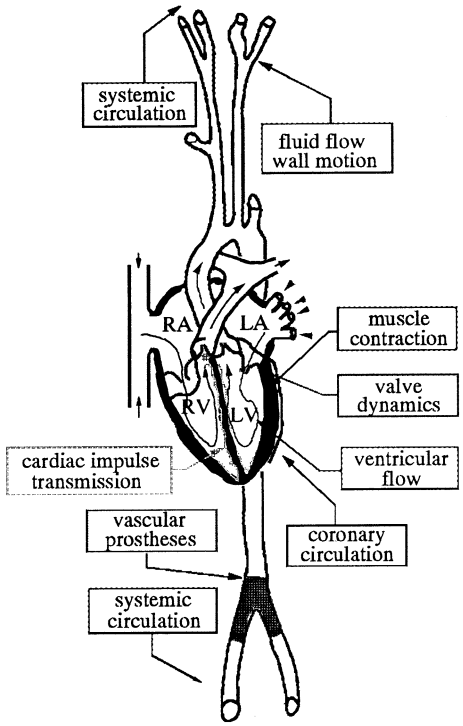

Figure 1. Schematic representation of the cardiovascular system.

atherogenesis. But, as shown by Zhao *et al.* [7], also specific strain distribution in the vessel wall may contribute to the development of atherosclerosis.

Another important pathology of the cardiovascular system, not always related to atherosclerosis, is what is called heart failure: an insufficient pump function of the heart often due to disturbed contraction patterns of the heart muscle. Stenosis or leakage of one or more of the heart valves, hypertension or a disturbed electrical activation of the heart muscle can cause heart failure.

2.2. Diagnostics and intervention

Diagnostic methods to detect atherosclerotic disease or heart failure are mainly based on imaging techniques like X-ray, CT, US and MRI and can provide excellent geometrical information and in some cases quantitative measures of blood flow. As mentioned above, especially wall strain and wall shear stress are important parameters. Stress distributions in particular can not be measured directly and must be assessed by combining diagnostic measurements with mathematical models that can predict stresses and strains. This combination of the outcome of diagnostic measurements and results of mathematical modelling is a strategy known as model- or simulation-based diagnostics.

Partial replacement, reconstruction and bypassing with a vascular prostheses or auto-grafts and balloon angioplasty with or without stent procedures are interventions often performed to treat atherosclerotic arteries. Not in all cases this kind of therapy is successful and restenosis is still a frequently occurring complication. Better knowledge of biochemical and mechanical interaction between prosthesis or stent with the vessel wall and blood flow is needed to increase the rate of success of these kinds of intervention. This includes the knowledge of the

material properties with respect to mechanical functioning and bio-compatibility. The same holds for mechanical, biological and in future also tissue-engineered heart-valve prostheses. A significant part of this knowledge can be obtained by means of *in-vitro* experimental and mathematical modelling. So in addition to its role in diagnostics, mathematical modelling is also important in the development and optimization of prostheses and medical devices.

Finally, mathematical models can be used for therapy selection and intervention planning. For example, in the case of heart failure, models that can describe the function and adaptation of the heart muscle, for instance as a result of changes in pre- and after-load, can be used to predict the effect of heart-valve replacement, application of cardiac-assist devices or use of artificial pacing. Also other examples where therapy selection is related to medical decision-making and surgical planning can be found in the literature [8].

As anatomy, morphology and material properties can vary significantly between different individuals, mathematical models should not only be suitable to give general information about physiological or pathological phenomena, but should also be suitable to provide patient-specific information that can be used to analyze the clinical picture of the individual patient and select a possible patient-specific therapy. In that case, to obtain patient-dependent data, mathematical modelling goes hand in hand with medical imaging and function measurements.

The above indicates that, for understanding patho-physiology of the cardiovascular system, for development and interpretation of diagnostic measurement methods and data, for design and optimization of prostheses and medical devices and for prediction of the outcome of medical intervention, knowledge of biomechanical aspects is of great importance. Either generic or patient-specific mathematical modelling is one of the means that can be used to accommodate this knowledge.

3. Mathematical models of the cardiovascular system

3.1. The complete system

A complete model of the cardiovascular system as depicted schematically in Figure 1 should be able to describe the pressure and flow waves in the pulmonary and systemic arterial system due to the contraction of the heart muscle as a function of pressure and volume of the heart chambers, all this dependent on the perfusion of the contractile myocardial tissue as provided by the coronary circulation. In this process the opening and closing dynamics of the heart valves as a result of pressure gradients over the valves and inertia forces related to the flow in the left ventricle is a complicating factor. In addition to this, the contraction mechanism is also determined by the electrical cardiac-impulse transmission. Finally, this set of systems is strongly influenced by central and local regulatory and adaptation mechanisms of the heart and arterial wall. Although many parts of the above-mentioned aspects with respect to mathematical modelling of the cardiovascular system are covered in several textbooks [9–12], much is still open for further research.

In summary, the mathematical modelling of the cardiovascular system is extremely complex and at the present time no model exists that is able to describe all the aspects mentioned above in their mutual relation. As a consequence we have to concentrate on a deliberate decoupling of functional parts. With respect to the mechanical function of these parts, the general concepts of mass, momentum and energy conservation applied for fluids and solids can be taken as a point of departure.

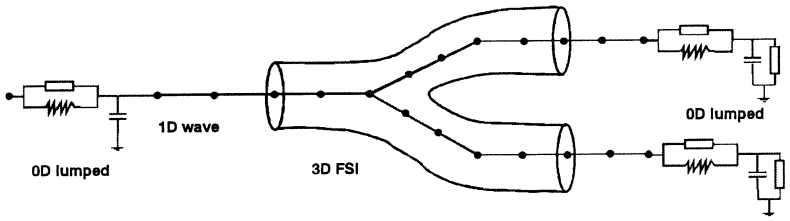

Figure 2. Schematic representation of decoupling by segmental dimension reduction.

3.2. GOVERNING EQUATIONS: FLUID AND STRUCTURE

The local velocity field of blood flow and the motion and deformation of the heart muscle, arterial wall and heart valves are completely described by the basic laws of mechanics, being conservation of mass and momentum. For fluids these laws can be expressed in equations of motion with the variables stress and velocity as functions of space and time. For solids the variables are mostly stress and displacement. At the interface between fluid and solid kinematic and dynamic constraints take care of the coupling. A closed set of differential equations is obtained if the constitutive behavior of the fluid (blood) and solid (cardiovascular tissue) can be expressed as a relation between stress and deformation and appropriate boundary conditions are defined. An important complication, and challenge for future research, is to incorporate regulation and adaptation mechanisms in the constitutive relations. Even for the most simple constitutive relations (*e.g.* a Newtonian fluid and linear elastic solid), the geometrical complexity of most cardiovascular systems of interest makes the solution or analysis of the set of equations a difficult task. Either advanced computational methods or mathematical analysis of idealized models have to be applied to obtain better understanding. In this special issue we can find contributions that are examples of one of the two strategies or a combination of them.

3.3. CONSTITUTIVE RELATIONS

3.3.1. *Blood*

Blood is not a homogeneous fluid but a suspension of blood cells, platelets, lipids and other constituents in plasma. Especially the red blood cells, normally occupying about 40% of the blood volume, strongly determine the constitutive behavior of blood. At low shear rate a network structure due to coagulation of red blood cells can form. At higher shear rate, like in the arteries, this network is broken and orientation and deformation of red blood cells will alter the viscous properties significantly. As to the forming and breaking down of the network, the deformation and the orientation of red blood cells are not expected to take place instantaneously, blood should be considered as a visco-elastic fluid. A combined experimental-numerical study of Gijsen *et al.* [13], however, showed that the time constants involved are such that formation of a network in normal blood flow does not take place and orientation and deformation occur so fast that inelastic nonlinear viscous models can be applied without loss of too much accuracy for flow in large arteries and veins.

3.3.2. *Cardiovascular tissue*

Vessel wall but also heart-valve tissue shows a strong nonlinear relation between stress and strain as a result of the anisotropic collagen-fiber structure embedded in the elastine matrix. At low strain these fibers are not fully stretched and the properties of the elastine matrix is

dominant. At high strains, the higher stiffness of the stretched collagen fibers dominates the elastic properties of the tissue. Experiments by van Oijen [14], using segments of human arteria axillaries, confirm data from the literature [15] and show that the mechanical behavior of vascular tissue can be described by an anisotropic fiber-reinforced material with a linear elastic matrix and nonlinear (exponential) stress-strain relation for the fiber.

The heart muscle can be described in a way similar to the vascular wall with the difference that now the fiber has an active component based, for instance, on a Hill model of sarcomere contraction where fiber stress depends on time, strain and strain rate (see [16, pp. 547–554]).

3.4. Decoupling by segmental dimension reduction

As indicated earlier, the cardiovascular system consist of a set of mutually connected systems with a strong coupling between their individual behavior. Decoupling of the system in segments is mostly impossible because in that case initial and especially boundary conditions for the decoupled segment are not known.

A better way of decoupling can be obtained by defining the initial and boundary conditions for a segment with the aid of a model covering a larger segment that is less complex and preferably of lower dimension. In practice this results in a coupling of 0D lumped parameter models with 1D wave-propagation models and finally with fully 3D fluid-structure interaction models (see Figure 2). In this issue examples of lumped-parameter, 1D wave propagation and fully 3D models will pass in review. A short overview of this is given in the next section.

4. Contents of this issue

4.1. Cardiac mechanics

In cardiac mechanics, research is focused on the understanding how the behavior of individual heart-muscle cells contributes to the contractile function of the complete heart as a function of its pre- and after-load. Lumped-parameter models as well as continuum models can be used for this purpose. Particular interest goes to the adaptation of the heart muscle to changes in mechanical load, for instance induced by cardiac arrest or pacemakers. Mathematical models for electrical conductance, excitation and muscle contraction can extend the value of diagnostic measurements and the planning of treatment of heart failure.

4.1.1. *Lumped-parameter models for heart-arterial interaction*

An illustrative example of the use of lumped-parameter models of the cardiovascular system is the heart-arterial interaction model of Segers *et al.* [17]. In this study a time-varying elastance model for ventricular contraction is coupled with a four-element windkessel model for the systemic circulation. Model parameters are fit to data obtained from animal experiments and the predictive value of the model as well as its clinical application is evaluated.

4.1.2. *Finite-element methods for heart-muscle contraction*

If local phenomena like those that occur in artificial pacing of the heart muscle are important, lumped-parameter models are not practical and continuum models can be used. Numerical methods like the finite-element method are then needed to obtain approximate solutions of the governing set of equations. The work of Kerckhoffs *et al.* [18] on ventricular electromechanics and pacing is a good example of such a finite-element-based continuum model and shows that

simulation models can give information valuable for planning of interventions like ventricular pacing.

4.2. 1D WAVE PROPAGATION AND FLOW IN BRANCHING TUBES

1D wave propagation models are based on the set of equations that result when the Navier-Stokes equations are integrated with respect to transversal cross-sections of the arteries and combined with a constitutive relation between local pressure and cross-sectional area. As long as geometrical changes are smooth and long waves are concerned, an accurate model for pressure and flow waves can be obtained in this way. At geometrical discontinuities like stenoses and branches, the 1D model can not be applied and more sophisticated models are needed.

4.2.1. *Wave-propagation models*

Wave-propagation of pressure and flow waves has been a subject of investigation for many years. A short review is given in the contribution of Sherwin *et al.* [19] and the *2003 James Lighthill Memorial Paper* written by Pedley [1]. After a relative silence in the late 80s and early 90s, when numerical methods for fully 3D analysis were developed, a renewed interest in 1D models is found because of their importance in the definition of boundary conditions for 3D fluid-structure interaction problems as indicated in the papers of Formaggia *et al.* [20] and wave-intensity analysis as mentioned in the contribution of Pedley.

4.2.2. *Pressure and flow at geometrical discontinuities and branches*

A 1D model for the complete arterial tree can be obtained by application of interface conditions at branches. Ways to define such interface conditions are given in the papers of Sherwin *et al.* [19] and Formaggia *et al.* [20]. References to more sophisticated analysis of flow at complex geometries and branches can be found in the paper of Pedley [1]. An example of such an analysis is the contribution of Smith *et al.* [21] on the modelling of fluid flow through branching tubes.

4.3. MECHANICAL AND MASS-TRANSFER MODELS RELATED TO ATHEROGENESIS

As mentioned earlier, the development of atherosclerotic disease may be correlated to vascular wall-shear-stress distribution and particle residence time of various molecules on the one hand and wall-strain distributions at the other. A key-role in this is attributed to the endothelium that is involved in processes like diameter regulation, prevention of blood coagulation and control of vascular permeability in mass transfer processes.

4.3.1. *Wall shear stress and wall strain*

The endothelium that lines the inner wall of the arteries is subjected to mechanical loads that originate from blood-flow-induced wall shear stress and pressure-wave-induced wall strain. In the paper of Kaazempur *et al.* [22] the pressure-induced cyclic strain that is experienced by the endothelial cells in the carotid bifurcation is analyzed and a potential correlation to atherogenesis is hypothesized.

4.3.2. *Mass transfer*

In addition to the importance of permeability influenced by the endothelium, the residence time and concentration of particles involved in the metabolic exchange between blood and vessel wall is of importance and may determine the characteristic time constants of the mass-transfer process. The residence time and particle concentration strongly depend on local flow phenomena. Although numerical simulations of mass transfer in complex artery geometries were published earlier [23], mathematical modelling to obtain better understanding of the parameters involved is not trivial. The analysis of shear-rate-dependent mass transfer in an idealized geometrical configuration of an injured region of the arterial wall is a topic discussed in the contribution by Heil and Hazel [24].

4.4. Fluid-structure-interaction models in relation with medical imaging

Another challenge in mathematical modelling of the cardiovascular system is to obtain models for the analysis and understanding of mechanical fluid-structure interaction and its application to cardiovascular prosthesis design, model-based diagnostics and surgery planning.

4.4.1. *Fluid-structure interaction*

A mathematical framework for computational methods based on weighted residual formulations of the equations of motion for fluid and solid is given in van de Vosse *et al.* [25]. Combination of arbitrary Lagrange-Euler and fictitious-domain methods offer the possibility to perform simulations of fluid flow in interaction with distensible structures (like arteries and the left ventricle of the heart) with other moving structures (like heart valves) immersed.

4.4.2. *Relation with medical imaging*

As shown in the contributions of Cebral *et al.* [26], Leuprecht *et al.* [27] and Zeng and Ethier [28], computational methods, with or without fluid-structure interaction, can be used for a variety of clinical applications, especially when combined with patient-specific data from imaging techniques like MRI. Examples are given for the the cerebral circulation by Cebral *et al.* [26], the aortic root by Leuprecht *et al.* [27] and the coronary circulation by Zeng *et al.* [28]. From the prospects given by these authors it can be derived that actual application of these computational methods in clinical practice is not trivial but may not be far off.

5. Discussion

In this introduction a broad outline of different, though surely not all, aspects of mathematical modelling of the cardiovascular system is given without the intention of presenting a complete review. It has been indicated that mathematical modelling is important for physiological understanding of the function of the cardiovascular system and for improved diagnostics and treatment of cardiovascular disease. Also, the sum of the contributions of this issue does not contain the complete field of cardiovascular mathematical modelling; yet a significant part of it is covered. The objectives of the studies presented in the papers that constitute this issue confirm the physiological and clinical relevance stated in this introduction and indicate that mathematical modelling significantly contributes to both fundamental and applied cardiovascular research. In view of the progress made and the increased applicability in clinical practice one may anticipate that it will do this even more in the future.

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