AN OVERVIEW OF SOME MATHEMATICAL MODELS OF BLOOD RHEOLOGY

Adélia Sequeira[1] and João Janela[2]

[1]*Dept. Matemática, IST and CEMAT/IST, Universidade Técnica de Lisboa, Av. Rovisco Pais, 1, 1049-001 Lisboa, Portugal; email: adelia.sequeira@math.ist.utl.pt*

[2]*Dept. Matemática, ISEG and CEMAT/IST, Universidade Técnica de Lisboa, Rua do Quelhas, 6, 1200 Lisboa, Portugal; email: jjanela@iseg.utl.pt*

Abstract: Experimental investigations over many years reveal that blood flow exhibits non-Newtonian characteristics such as shear-thinning, viscoelasticity and thixotropic behaviour. The complex rheology of blood is influenced by numerous factors including plasma viscosity, rate of shear, hematocrit, level of erythrocytes aggregation and deformability. Hemodynamic analysis of blood flow in vascular beds and prosthetic devices requires the rheological behaviour of blood to be characterized through appropriate constitutive equations relating the stress to deformation and rate of deformation.

The objective of this paper is to present a short overview of some macroscopic constitutive models that can mathematically characterize the rheology of blood and describe its known phenomenological properties. Some numerical simulations obtained in geometrically reconstructed real vessels will be also presented to illustrate the hemodynamic behaviour using Newtonian and non-Newtonian inelastic models under a given set of physiological flow conditions.

Keywords: Blood rheology, shear-thinning fluid, generalized Newtonian model, viscoelasticity, pressure pulse, wall shear stress.

1. INTRODUCTION

Mathematical and numerical models together with computer simulations are playing an increasingly relevant role in biology and medicine. Applications to blood flow in the human circulatory system and to its inherent pathologies, are certainly one of the major mathematical challenges of the coming decades.

Blood performs the essential functions of delivering oxygen and nutrients to all tissues, it removes waste products and defends the body against infection through the action of antibodies. Blood is a multi-component mixture

M. Seabra Pereira (ed.), A Portrait of State-of-the-Art Research at the Technical University of Lisbon, 65–87.

with complex rheologic characteristics which interacts both mechanically and chemically with vessel walls, giving rise to complex fluid-structure interaction models whose mathematical analysis is still incomplete and which are difficult to simulate numerically in an efficient manner. The blood circulation in the cardiovascular system depends not only on the rheology of blood itself but also on the driving force of the heart and the architecture and mechanical properties of the vascular system. Hemodynamic factors such as flow separation, flow recirculation, or low and oscillatory wall shear stress are now recognised as playing an important role in the localization and development of arterial diseases. They can have useful applications in medical research, surgical planning and therapy to restore blood flow in pathological organs and tissues. For instance, in the case of atherosclerosis numerous investigations report that the genesis and the progression of the disease are related with the locally complex and multi-directional flow field in the vicinity of curvatures, branches and bifurcations of large and medium sized vessels. The combined effects of complex arterial geometry with flow pulsatility and rheology induce low oscillating wall shear stress, high pressure distribution and a enhanced particle residence time in flow separation and flow recirculation zones, resulting in a locally distributed mass transfer (see e.g. **[6, 34, 41]**).

In contrast to vessel obstruction resulting from atherosclerotic disease, aneurysmal disease results in vessel enlargement and in some cases rupture. It is currently believed that the most important factors in the genesis of abdominal or cerebral saccular aneurysms (found in and about the circle of Willis) are congenital defects in the artery along with the thrust of pulsatile blood flow at these weak branched or bifurcating points (see e.g. **[9, 56]**).

Clinically relevant hemodynamic parameters, including pressure, velocity, blood flow patterns and shear stress, can be directly or indirectly quantified. Experimental measurements of blood flow velocity and pressure fields are very important in the diagnosis and surgical planning therapies of patients with congenital and acquired cardiovascular diseases. *In vivo* and *in vitro* experimental methods for quantifying these hemodynamic parameters involve both invasive and non-invasive techniques such as intra-vascular ultrasound probes **[33]**, electromagnetic flow probes **[45]** or Magnetic Resonance Imaging (MRI) **[52]**. The corresponding collected data are accurate enough for quantification of some aspects of the arterial diseases but are very sensitive to disturbing factors. This results in difficult interpretations in most relevant cases.

The development of effective and accurate numerical simulation tools to better understand local hemodynamics can play a crucial role in this process. Besides their employment in medical research, numerical models of vascular flows can provide a virtual experimental environment to be used as

a training system. For instance, techniques currently used to open narrowed atherosclerotic arteries are angioplasty (also called balloon angioplasty) and vascular stenting, which are minimally invasive procedures performed by an interventional radiologist to improve blood flow in the body's arteries. In the angioplasty procedure, the physician threads a balloon-tipped catheter (a thin, plastic tube) to the site of a narrowed or blocked artery and then inflates the balloon to open the vessel. The balloon is then deflated and removed from the artery. Vascular stenting, which is often performed at the same time as an angioplasty, involves the placement of a small wire mesh tube called a stent in the newly opened artery. This may be necessary after some angioplasty procedures to prevent recoil of the vessel after removal of the balloon. Currently there is much excitement in the cardiology community about drug–eluting stents which are a promising new treatment for coronary artery disease. This ingenious therapy involves coating the outer aspect of a standard coronary stent with a thin polymer containing medication that is released after implantation, dramatically decreasing the chance of restenosis at the site of treatment. However these medical techniques are largely empirical, they are related to the specific patient and their success depends mostly on the surgeon's decision and practice. Currently, using intravascular ultrasound, it is possible to obtain both intra pressure waves downstream and upstream the vascular constriction, as well as the velocity profiles of blood flow in the arteries, and build a 3D model of the local artery circulation. It is also possible to obtain data from patients with different diseases, such as variability in heart rate and reflex control of the circulation, both baro and chemoreflex. These data sets can be used to validate relevant hemodynamic flow quantities and generate metrics of disease state that will provide the design of algorithms for patient specific treatment strategies. The outcome of this new technique of the clinical practice is to develop a computer-aided surgical planning in a grid-supported virtual environment and is referred to as "predictive medicine" (see **[46]**). These are just a few examples of medical problems and procedures where computer simulations based on models of blood rheology play a major role.

Blood is a suspension of cellular deformable components (red blood cells, white blood cells and platelets) in plasma containing proteins, lipids, electrolytes and other matter. The study of blood flow in the vascular system is complicated in many respects and thus simplifying assumptions are often made. In the large vessels ($1 - 3cm$ of diameter) where shear rates are high enough, it is reasonable to assume that blood has a constant viscosity and a Newtonian behaviour. Numerical blood flow studies in these vessels are usually based on the Navier–Stokes equations with an appropriate constant reference viscosity. However in smaller vessels (arteries and arterioles, or veins and venules, with $0.2mm$ to $1cm$ of diameter) or in some diseased

conditions (like hypertension or atherosclerosis, among others) the presence of the cells induces low shear rate ($0.1s^{-1}$) and blood exhibits remarkable non-Newtonian properties, like shear-thinning viscosity and viscoelasticity, mainly due to red blood cells aggregation and deformability as reported by many authors (see details below, on Section 2). At the smallest levels (capillaries) blood cannot be modelled anymore as a homogeneous fluid, since the dimension of the particles are now of the same order of that of the vessels and the effect of wall permeability becomes also important.

In this work we assume that all macroscopic length and time scales are sufficiently large compared to those of blood formed elements. Thus the models presented here would not be appropriate in the capillary network. For an overview of hemorheology in the microcirculation we refer the reader to the review articles of Popel and Johnson **[36]**, Pries and Secomb **[37]** and Cristini and Kassab **[17]**.

The word hemorheology was introduced by A. L. Copley in a survey on rheology of blood in 1952, **[15]**. He defined the term as follows: 'Hemorheology is concerned with the deformation and flow properties of cellular and plasmatic components of blood in macroscopic, microscopic and submicroscopic dimensions, and in the rheological properties of the vessel structure which directly comes in contact with blood'. Additionally, A. L. Copley and G. Seaman **[16]** widened this definition saying that: 'Hemorheology is also the study of the interaction of blood or its components and the vascular system with added foreign materials, such as drugs, plasma expanders or prosthetic devices. Thus hemorheology is the study of how the blood and the blood vessels can function and interact as parts of the living organism'.

Clinical hemorheology deals with pathological hemorheological abnormalities and has developed based on the evidence that the change of rheological properties of blood and its components might be the fundamental cause of many cardiovascular diseases. Hemorheological alterations can easily be considered as a result (or an indicator) of insufficient circulatory function. Alternatively, alterations in hemorheological parameters may affect tissue perfusion and be manifested as circulatory problems. Basically, pathologies with hematological origin like leukemia, hemolytic anemia, thalassemia or pathologies associated with the risk factors of thrombosis and atherosclerosis like myocardial infarction, hypertension, strokes or diabetes are mainly related to disturbances of local homeostasis. Therefore the mathematical and numerical study of powerful, yet simple, constitutive models that can capture the rheological response of blood over a range of flow conditions is ultimately recognised as an important tool for clinical diagnosis and therapeutic planning (see e.g. **[29]**).

This paper is organized as follows. In the next sections we give a short description of the main rheological properties of blood, followed by an outline

of various macroscopic constitutive models based on its mechanical properties. Finally, we present the results of some numerical simulations using a finite element approach of non-Newtonian inelastic fluid models, to show the importance of the rheology of blood under a given set of physiological flow conditions.

2. BLOOD MORPHOLOGY AND VISCOMETRIC PROPERTIES

Blood is a multi-component mixture with complex rheological characteristics. It consists of multiple cellular elements: (i) red blood cells – RBCs (erythrocytes), the most numerous of the formed elements (about 98%) are tiny biconcave discoid particles, filled with a fluid, which are involved in oxygen and carbon dioxide transport; (ii) white blood cells – WBCs (leukocytes) are much less numerous than RBCs, they have nuclei, and are classified into two groups: granulocytes and agranulocytes. Leukocytes are involved in the organism's defence against invasion by bacteria and viruses and, as well as erythrocytes are formed from stem cells in the bone marrow; (iii) platelets (thrombocytes), small discoid cell fragments containing various chemicals such as serotonin, thrombin, ADP, are much smaller than erytrocytes (approximately $6\mu m^3$ in size as compared to $90\mu m^3$) and form a small fraction of the particulate matter of human blood (around 3% by volume). Platelets get activated due to several biochemical reactions and mechanical processes and are involved in the formation of clot cascades (see more details in Section 2.2), but they have a negligible effect on the mechanics of normal blood, compared to erythrocytes.

The cellular elements are suspended in an aqueous polymer solution, the plasma, containing electrolytes as well as organic molecules such as metabolites, hormones, enzymes, antibodies and other proteins and representing approximately 55% of the blood volume. Plasma transports nutrients as well as wastes throughout the body.

White blood cells are normally roughly spherical in shape, with the diameters ranging from about 7–22 μm. Rather little is known of the mechanical properties of the WBCs. It has been argued that they are stiffer than RBCs, because in a collision between a red and a white cell in flowing blood, it is the former which mainly deforms.

We focus particular attention on the red blood cells because they are the only cells which significantly influence the mechanical properties of blood. They do this because they are present in very high concentration (approximately $5 \times 10^6/mm^3$) comprising about 40 to 45% of its volume (hematocrit). The rheology of blood is therefore primarily determined by the behaviour of the erythrocytes at different shear rates.

2.1 Blood viscosity and viscoelasticity

When a suspension of randomly distributed particles (be they rigid, deformable or fluid) is flowing in an apparatus whose dimensions are large compared to those of the particles and the space between them, the mixture can be regarded as a homogeneous fluid. By studying the mechanical properties of such a suspension, we can see what determines its viscosity and whether it has a Newtonian (shear stress proportional to the rate of shear) or non-Newtonian behaviour.

As already referred red blood cells are highly flexible biconcave discs (some 8.5 μm in diameter) with a very thin membrane (2.5 μm of maximum thickness) and filled with a saturated solution of hemoglobin, which are capable of extreme distortion, without changing their surface area, as when they travel along capillaries with diameters smaller than their own. Another phenomenon closely linked to the deformability of the RBCs is the rotation of the membrane around the liquid interior in a shear flow (tank-threading movement, **[7]**). At sufficiently low shear rates (smaller than $10s^{-1}$) RBCs tend to aggregate attaching side-by-side and forming long clusters called *rouleaux*, see Figure 1. Under no flow conditions, the time scale for the formation of these aggregates is $60s$. If shear rate is decreased even further, to $1s^{-1}$, the rouleaux form long column-like structures, inducing an additional increase of the viscosity. The time required for building a network is even longer than for rouleaux formation. This mechanism is still incompletely understood. It appears that the erythrocytes attract one another and the process depends in particular on the influence of bridging macromolecules, especially fibrinogen and globulins in the plasma. The process will not occur in their absence and it occurs progressively faster with increasing concentration of these macromolecules **[5]**. If shear rate is increased, and is high enough, the rouleaux break up, RBCs deform into an infinite variety of shapes without changing volume, they align with the flow field and tend to slide upon plasma layers formed in between. This induces the decrease of the blood viscosity. Deformability, orientation and aggregation of red blood cells result in shear-thinning viscosity of blood (Figure 2). It should be added, however, that other non-Newtonian phenomena occur in small sized vessels, such as the Fåhraeus-Lindqvist effect **[20]** (cell alignement and plasma skimming), Fåhraeus effect **[19]** (dymanic reduction of hematocrit in small vessels) and sedimentation, reducing the apparent viscosity of blood in the microvessels (see e.g. **[17, 36, 37]**).

Since blood cells are essentially elastic membranes filled with a fluid, it seems reasonable, at least under certain flow conditions, to expect blood to behave like a viscoelastic fluid. At low shear rates RBCs aggregate and are ‘solid-like’, being able to store elastic energy that accounts for the memory

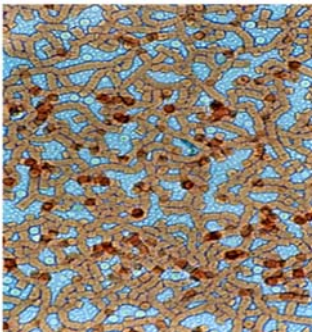

Figure 1. Profile view of erythrocytes forming rouleaux (courtesy of Prof. M.V. Kameneva, University of Pittsburgh, USA).

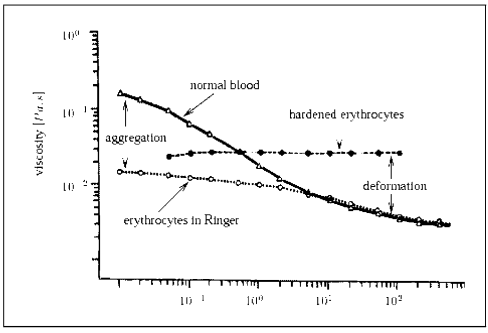

Figure 2. Viscosity in steady shear of normal blood, blood with hardened erythrocytes (no deformation) and blood in a Ringer solution (no aggregation), from Chien et al. **[12]** and Caro et al. **[6]**.

effects in blood. Dissipation is primarily due to the evolution of the RBC networks and, given the paucity of data on temperature effects, the internal energy is assumed to depend only on the deformation gradient. At high shear rates, the RBCs disaggregate forming smaller rouleaux, and later individual cells, that are characterized by distinct relaxation times. RBCs become 'fluid-like', losing their ability to store elastic energy and the dissipation is primarily due to the internal friction. Upon cessation of shear, the entire rouleaux network is randomly arranged and may be assumed to be isotropic with respect to the current natural configuration. Thurston (see **[48]**) was among the earliest to recognize the viscoelastic nature of blood and that the viscoelastic behaviour is less prominent with increasing shear rate. He investigated viscoelastic properties of blood in the linear viscoelastic regime and measured a significant elastic component in oscillatory blood flow. He also measured the shear rate dependence of the viscoelastic properties of blood at a given frequency **[49]**. From these measurements, the non-linear viscoelastic properties of blood are evident.

It also been experimentally observed that aggregation, break down of *rouleaux* and orientation of RBCs take place over different non-zero time scales. McMillan et al. **[30]** investigated the transient properties of blood in viscometric flow and measured shear stress generated by blood at different shear rates. These authors verified a delayed relaxation of shear stress but they could not detect any measurable first normal stress differences in blood. Based on these results, blood can also be considered thixotropic at low shear rates **[25]**.

The rheological behaviour of blood is mainly governed by the concentration and the properties of the red blood cells, as mentioned above. The deformability, orientation and aggregation of RBCs induce the specific be-

haviour of blood in simple shear flow. Using viscometers, a uniform velocity field is generated and by measuring the flow induced torque, the viscometric properties of blood can be determined. However, due to inhomogenities of blood and its complex behaviour, the determination of the viscometric properties of blood is complicated and results from literature should be interpreted with caution. For an extended review on the technical problems that arise when the properties of blood are determined through viscometry, see e.g. Cokelet **[14]**.

2.2 Platelet activation and blood coagulation

While there has been a considerable research effort in blood rheology, the constitutive models have thus far focused on the aggregation and deformability of the RBCs, ignoring the role of platelets in the flow characteristics. However they are by far the most sensitive of all the components of blood to chemical and physical agents, and play also a significant role in blood rheology.

The hemostatic system is maintained in a state of readiness to respond immediately to vascular injuries due to the perforation of the vessel wall, activation of endothelium by chemicals or inflammatory processes. This high reactivity can inevitably result in the initiation of clotting and the threat of thrombosis. Blood platelets participate in both hemostasis and thrombosis by adhering to damaged vessels and by getting activated releasing chemicals (activators responsible for the blood coagulation cascade) into the blood plasma. They can induce other platelets to become activated and to aggregate and, once the activated platelets bind with the sub-endothelium, the aggregate interacts with fibrin to form irreversible hemostatic plugs (*thrombi*). Prior to this, however, platelet aggregates that are formed by this process can break up (when the concentration of activators exceeds a certain value), damaging the platelets and causing aggregation at locations different from the site of damage. Arterial occlusion, acute myocardial infarction, venous thrombosis and most strokes are some of the pathological processes related to platelet activation.

Understanding these processes is an issue of major medical importance. Numerous clinical and experimental studies recognized that thrombus formation occurs not in regions of parallel flow, but primarly in regions of stagnation point flows, within blood vessel bifurcations, branching and curvatures. Moreover, internal cardiovascular devices such as prosthetic heart valves, ventricular assisting devices and stents, generally harbor high hemodynamic shear stresses that can cause platelet activation. Thrombotic deposition encountered in these devices is a major cause of their failure and of the pathological effects mentioned above. A reliable model that can predict regions of

platelet activation and deposition (either in artificial devices or in arteries), has the potential to help optimize design of such devices and also identify regions of the arterial tree susceptible to the formation of thrombotic plaques and possible rupture in stenosed arteries.

The mechanism of platelet activation and blood coagulation is quite complicated and not yet completely well understood. Recently, Kuharsky and Fogelson **[28]** have developed a model consisting of 59 first order ODEs that combines a fairly comprehensive description of coagulation biochemistry, interactions between platelets and coagulation proteins and effects of chemical and cellular transport. They assume that all reactions occur in a thin layer shell above the injured surface and the constants and concentrations used in the models are only based on those available in the literature (no curve fitting was done). This model, as well as previous work developed along these lines (see e.g. **[21, 27, 55]**) can be considered as an important achievement to capture many of the biochemical aspects of the problem. However, they do not allow for the realistic hydrodynamical and rheological characteristics of blood flow in vessels whose geometry is made complex by the presence of wall-adherent platelets or atherosclerotic plaques. A phenomenological model introduced by Anand and Rajagopal **[1, 2]** can be considered as the first approach to address this oversight. This last paper features an extensive bibliography on the subject.

3. BLOOD CONSTITUTIVE MODELING

In large and medium sized vessels blood can be modelled as an homogeneous incompressible Newtonian fluid, with flow behaviour described by the time-dependent Navier–Stokes equations. These equations are derived from the conservation of linear momentum and mass (incompressibility condition) and, in a general form, they read

$$\rho\frac{\partial \boldsymbol{u}}{\partial t} + \rho(\boldsymbol{u}\cdot\nabla)\boldsymbol{u} = \nabla\cdot\boldsymbol{\sigma} + \boldsymbol{f}, \qquad \nabla\cdot\boldsymbol{u} = 0 \quad \text{in } \Omega_t \subset \mathbb{R}^3, \quad t \in (t_0, T) \tag{1}$$

where Ω_t is an open bounded set, representing the interior of a vessel at time t, with a sufficiently regular boundary denoted by Γ_t composed of Γ_t^w, Γ_t^{in} and Γ_t^{out} the vessel lateral wall, inlet boundary and outlet boundary, respectively. The convective term is

$$(\boldsymbol{u}\cdot\nabla)\boldsymbol{u} = \sum_{j=1}^{3} u_j \frac{\partial}{\partial x_j}\boldsymbol{u}. \tag{2}$$

Here $\boldsymbol{u}$ denotes the flow velocity vector, ρ is the constant fluid density and **f** are the external body forces per unit volume (e.g. gravity). The Cauchy

stress tensor $\boldsymbol{\sigma}$ is expressed as the combination of an isotropic pressure p and the viscous contribution

$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\eta \boldsymbol{D} \tag{3}$$

where η is a constant dynamic viscosity and $\boldsymbol{D}$ is the rate of deformation tensor defined by

$$\boldsymbol{D} = \frac{1}{2}\left(\nabla \boldsymbol{u} + (\nabla \boldsymbol{u})^T\right). \tag{4}$$

The system of equations (1) must be closed by imposing appropriate initial and boundary conditions. This usually reduces to prescribing either the velocity field or tangential and normal components of the stress vector in Γ^{in} and Γ^{out}. We prefer to consider the flow as being driven by a pressure drop, but this must be done in a careful way since only for fully developed outflow velocities a prescribed normal component of the stress vector (together with zero tangential velocity) corresponds to a prescribed pressure.

In cases where the vessel is not assumed to be rigid these equations are generally rewritten using the ALE (Arbitray-Lagrangean-Eulerian) formulation that is more suitable for moving domains. When considering the full fluid-structure interaction problem with the vessel walls, a model must be specified for the structure and convenient interface conditions in the solid-fluid interface.

As already pointed out blood is essentially a non-Newtonian fluid and the constitutive equations for blood must incorporate the non-linear viscometric properties of blood previously discussed. In this section we present a review on the macroscopic constitutive models that can mathematically characterize the rheology of blood and describe its known phenomenological properties, especially the shear-thinning and viscoelastic behaviour. The corresponding non-Newtonian constitutive equations are subdivided into generalized Newtonian or inelastic models and viscoelastic models.

3.1 Generalized Newtonian models

We start from the constitutive assumption that the Cauchy stress tensor $\boldsymbol{\sigma}$ only depends on the fluid mass density and the velocity gradient, meaning that the current state of stress depends only on the velocity gradient at the current time and not on the history of deformations the fluid may have undergone in the past. If we further demand invariance under a superposed rigid motion, using a representation theorem for isotropic symmetric tensor functions, it can be shown that the most general form $\boldsymbol{\sigma}$ can assume is

$$\boldsymbol{\sigma} = \phi_0 \mathbf{I} + \phi_1 \boldsymbol{D} + \phi_2 \boldsymbol{D}^2 \tag{5}$$

where $\boldsymbol{D}$ is the symmetric part of the velocity gradient (4) and ϕ_0, ϕ_1, ϕ_2 depend on the density ρ and on the three principal invariants of $\boldsymbol{D}$, $I_D = tr(\boldsymbol{D})$, $II_D = ((tr\boldsymbol{D})^2 - tr(\boldsymbol{D}^2))/2$ and $III_D = det(\boldsymbol{D})$. Using the same arguments for incompressible fluids for which the stress tensor only depends on the velocity gradient, it can be seen that the stress tensor must be of the form

$$\boldsymbol{\sigma} = \alpha\mathbf{I} + \phi_1\boldsymbol{D} + \phi_2\boldsymbol{D}^2 \tag{6}$$

where α is a Lagrange multiplier connected to the incompressibility constraint and ϕ_1, ϕ_2 only depend on II_D and III_D. These fluids are generally known has *Reiner-Rivlin fluids*. If $\phi_2 = 0$ and ϕ_1 is constant, we recover the classical Newtonian fluids. On the other hand Reiner-Rivlin fluids with $\phi_2 \neq 0$ don't match any experimental results under simple shear. Finally, if we consider that the dependence of ϕ_1 on III_D is negligible, we obtain the so called *Generalized Newtonian fluids*. Thermodynamic considerations and the analysis of their behaviour under simple shear (and other viscometric flows) leed to the final form of $\boldsymbol{\sigma}$

$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\eta(\dot{\gamma})\boldsymbol{D} \tag{7}$$

where $\dot{\gamma} := \sqrt{2\boldsymbol{D} : \boldsymbol{D}}$ is the shear rate. Generalized Newtonian models differ only on the functional dependence of the non-Newtonian viscosity η, on the shear rate. Each model involves a number of parameters that allow for fitting to experimental data of the fluid under analysis.

Table 1 summarizes some of the most common generalized Newtonian models that have been considered for the shear-dependent viscosity of whole human blood (see Cho and Kensey **[13]**).

In these models the constants η_0 and η_∞ are the asymptotic viscosities at zero and infinity shear rates, i.e.

$$\eta_0 = \lim_{\dot{\gamma}\to 0} \eta(\dot{\gamma}), \quad \eta_\infty = \lim_{\dot{\gamma}\to \infty} \eta_(\dot{\gamma}),$$

n is the power index and λ are parameters determined by numerical fitting of experimental data.

Attempts to recognize the shear–thinning nature of blood were initiated by Chien et al. **[10, 11]** in the 1960s. Empirical models like the power-law (or Walburn-Schneck power-law **[54]**, with constants related to hematocrit and the content of protein minus albumin), Cross **[18]**, Carreau **[8]**, Carreau–Yasuda or modified models **[53]** were seen to agree well in their predictions and were preferred over the power-law model which has an unbounded viscosity at zero shear-rate. The main advantage of simpler models like power-law is that there are exact solutions available in some geometries and flow conditions, providing natural benchmarks for the numerical codes. For a recent survey and experimental tests on several inelastic constitutive models

Table 1. Comparison of various Generalized Newtonian models for blood.

Model	non-Newtonian viscosity	model constants for blood
Power-Law	$\eta(\dot{\gamma}) = k\dot{\gamma}^{n-1}$	$n = 0.61, k = 0.42$
Powell-Eyring	$\frac{\eta(\dot{\gamma}) - \eta_\infty}{\eta_0 - \eta_\infty} = \frac{sinh^{-1}(\lambda\dot{\gamma})}{\lambda\dot{\gamma}}$	$\eta_0 = 0.056Pas, \eta_\infty = 0.00345Pas$ $\lambda = 5.383s$
Cross	$\eta(\dot{\gamma}) = \eta_\infty + \frac{\eta_0 - \eta_\infty}{1 + (\lambda\dot{\gamma})^m}$	$\eta_0 = 0.056Pas, \eta_\infty = 0.00345Pas$ $\lambda = 1.007s, m = 1.028$
Modified Cross	$\eta(\dot{\gamma}) = \eta_\infty + \frac{\eta_0 - \eta_\infty}{(1 + (\lambda\dot{\gamma})^m)^a}$	$\eta_0 = 0.056Pas, \eta_\infty = 0.00345Pas$ $\lambda = 3.736s, m = 2.406, a = 0.254$
Carreau	$\frac{\eta(\dot{\gamma}) - \eta_\infty}{\eta_0 - \eta_\infty} = (1 + (\lambda\dot{\gamma})^2)^{(n-1)/2}$	$\eta_0 = 0.056Pas, \eta_\infty = 0.00345Pas$ $\lambda = 3.313s, n = 0.3568$
Carreau–Yasuda	$\frac{\eta(\dot{\gamma}) - \eta_\infty}{\eta_0 - \eta_\infty} = (1 + (\lambda\dot{\gamma})^a)^{(n-1)/a}$	$\eta_0 = 0.056Pas, \eta_\infty = 0.00345Pas$ $\lambda = 1.902s, n = 0.22, a = 1.25$

for blood, see **[58]**. Also the belief that blood demonstrates a yield shear stress led to one of the simplest constitutive models for blood, the Casson's equation (see **[44]**), which is valid only over a small range of low shear rates and in steady flow. The evidence for yield stress in blood is circunstantial and there is no consensus about its value. However, none of the above homogeneized models are capable of describing the viscoelastic response of blood.

3.2 Viscoelastic models

A simple way to account for the elastic effects in a non-Newtonian fluid is to consider the constitutive equation for the Maxwell fluid given by

$$\boldsymbol{S} + \lambda_1 \overset{\nabla}{\mathbf{S}} = 2\mu_0 \boldsymbol{D}, \qquad \boldsymbol{\sigma} = -p\mathbf{I} + \boldsymbol{S} \tag{8}$$

where $\boldsymbol{S}$ is the extra-stress tensor and $^\nabla$ stands for the upper-convected derivative of a tensor field

$$\overset{\nabla}{\mathbf{S}} = \frac{\partial \boldsymbol{S}}{\partial t} + (\boldsymbol{u} \cdot \nabla)\boldsymbol{S} - \boldsymbol{S} \cdot \nabla \boldsymbol{u} - (\nabla \boldsymbol{u})^T \cdot \boldsymbol{S} \tag{9}$$

The constant $\lambda_1 > 0$ is the stress relaxation time (the larger is λ_1, the slower is relaxation) and the material constant μ_0 is the (zero shear rate) viscosity coefficient.

A more general class of rate type models, the so-called *Oldroyd-type models*, can be defined by

$$\boldsymbol{S} + \lambda_1 \overset{\nabla}{\mathbf{S}} = 2\mu_0(\boldsymbol{D} + \lambda_2 \overset{\nabla}{\mathbf{D}}) \tag{10}$$

where λ_2 is the relaxation time, with $0 \leq \lambda_2 < \lambda_1$.

The computational approach makes use of a decomposition of the total extra-stress tensor $\boldsymbol{S}$ into its non-Newtonian (polymeric) $\boldsymbol{S}_1$ and Newtonian (solvent) $\boldsymbol{S}_2$ parts such that

$$\boldsymbol{S} = \boldsymbol{S}_1 + \boldsymbol{S}_2. \tag{11}$$

The corresponding stress relations become

$$\boldsymbol{S}_1 + \lambda_1 \overset{\nabla}{\mathbf{S}} = 2\mu_1 \boldsymbol{D}, \tag{12}$$

$$\boldsymbol{S}_2 = 2\mu_2 \boldsymbol{D}, \tag{13}$$

where μ_1 is the elastic viscosity and μ_2 the Newtonian viscosity. It can be shown that

$$\mu_0 = \mu_1 + \mu_2 \quad \text{and} \quad \lambda_2 = \mu_2 \lambda_1 / \mu_0. \tag{14}$$

If $\lambda_2 = 0$ the model reduces to the upper-convected Maxwell fluid (8), while if $\lambda_1 = \lambda_2 = 0$ it is a purely Newtonian fluid (3) with viscosity μ_0.

By substituting relations (11) and (13) into the constitutive equation (10) and taking into account the conservation of linear momentum and mass, the equations of motion of an Oldroyd-B fluid can be written as

$$\begin{aligned} &\rho\left(\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u}\cdot\nabla)\boldsymbol{u}\right) - \mu_2 \Delta \boldsymbol{u} + \nabla p = \nabla \cdot \boldsymbol{S}_1, \quad \nabla \cdot \boldsymbol{u} = 0 \\ &\boldsymbol{S}_1 + \lambda_1\left(\frac{\partial \boldsymbol{S}_1}{\partial t} + \boldsymbol{u}.\nabla \boldsymbol{S}_1 - \boldsymbol{S}_1 \cdot \nabla \boldsymbol{u} - \nabla \boldsymbol{u}^T \cdot \boldsymbol{S}_1\right) = 2\mu_1 \mathbf{D} \end{aligned} \tag{15}$$

in $\Omega_t \subset \mathbb{R}^3$, with $t \in (t_0, T)$.

The governing equations of an Oldroyd-B model are of mixed parabolic-hyperbolic type. To close the system initial and boundary conditions must be given. In this case the boundary conditions are the same as for the Navier–Stokes equations, supplemented by the specification of the stress components at the inlet boundary. Usually the constitutive equations of non-Newtonian viscoelastic fluids of differential or rate type lead to highly non-linear systems of partial differential equations of this kind (parabolic-hyperbolic for unsteady flows and elliptic-hyperbolic for steady flows) and specific techniques of non-linear analysis, such as fixed-point arguments associated to auxiliary linear sub-problems are required to study the behaviour

of their solutions in different geometries. The mathematical and numerical analysis of non-Newtonian fluid models is a very rich field of research, with many fascinating problems (see e.g. **[31, 43]**).

As already referred in Section 2.1 various attempts have been made to recognize the viscoelastic nature of blood at low shear rates. Thurston **[48]** proposed a generalized Maxwell model that was applicable to one dimensional flow simulations and observed later that, beyond a critical shear rate, the non-linear behaviour is related to the microstructural changes that occur in blood (see **[49, 51]**). Quemada **[38]** also derived a non-linear Maxwell type model involving a first order kinetic equation used to determine a structural parameter related with the viscosity. Phillips and Deutsch **[35]** proposed a three-dimensional frame invariant Oldroyd-B type model with four constants which could not capture the shear-thinning behavior of blood throughout the range of experimental data. Other rate-type constitutive models for describing blood rheology have been proposed in the recent literature. Yeleswarapu **[57]** has obtained a three constant generalized Oldroyd-B model by fitting experimental data in one-dimensional flows and generalizing such curve fits to three dimensions. It captures the shear-thinning behaviour of blood over a large range of shear rates but it has limitations, given that the relaxation times do not depend on the shear rate, which does not agree with experimental observations. A variant of this model, which also includes a shear-thinning viscosity function has been proposed and studied by Arada and Sequeira **[4]**. The model recently developed by Anand and Rajagopal **[3]** in the general thermodynamic framework of Rajagopal and Srinivasa **[40]** includes relaxation times depending on the shear rate and gives good agreement with experimental data in steady Poiseuille flow and oscillatory flow. Finally we also refer to a recent shear-thinning, viscoelastic and thixotropic model related to the microstructure of blood, derived by Owens **[32]**. This model is inspired on the classical theory of transient networks for viscoelastic fluids and their predictions compare well with experiments for simple shear flows.

4. SOME NUMERICAL SIMULATIONS

Numerical simulation is an important tool for prediction of non-Newtonian phenomena. In the last two decades, intensive research has been performed in this area, mainly for differential and rate-type models **[31]**. The hyperbolic nature of the constitutive equations is responsible for many of the difficulties associated with the numerical simulation of viscoelastic flows. Some factors including singularities in the geometry, boundary layers in the flow and the dominance of the non-linear terms in the equations, result in numerical instabilities for high values of the Weissenberg number (non-dimensional number related with the elasticity of the fluid). Numerical

schemes used for solving these complex systems of PDEs must be based on a deep understanding of the mixed mathematical structure of the equations, in order to prevent numerical instabilities on problems that are mathematically well-posed. Discretizations in space are usually performed with Galerkin methods (Petrov-Galerkin or generalized Galerkin) or by collocation, reducing the problems to finite dimensional spaces. These choices are involved in the finite element method (conforming, non-conforming, mixed or hybrid), in the spectral method (Legendre or Chebychev expansion) or in the finite volume method. Finite difference and fractional-step schemes are generally used for marching in time (see e.g. **[39]**). All these methods lead to the solution of algebraic systems, typically very large, that are solved using direct or iterative methods. The solution of these algebraic systems often requires the use of preconditioners that can be regarded as operator projections, multigrid or domain decomposition methods. The major difficulties in many numerical schemes are related to the large amount of computation involved and to the loss of convergence or stability. This is the object of active research in the field.

4.1 Geometric reconstruction and mesh generation

Relevant blood flow simulations must be able to incorporate patient specific data. Since hemodynamics depends heavily on the geometry, it is important to run the numerical simulations on realistic geometries coming from medical imaging. The most common medical imaging technique presently used to obtain 3D representations of the human body is magnetic resonance (MR). The images obtained with this technique (MRI) are density plots of sucessive cross-sections of the area under investigation. Many algorithms using for instance levelset theory were developed to identify lines in these cross-sections, resulting in images like the one shown in Figure 3. Nowadays, fast and accurate scanning devices (e.g. magnetic resonance) are widely available for engineering and biomedical applications. The challenge is not to collect the data but to be able to translate them into something usable in computer simulations. On the other hand, discrete data resulting from this image acquisition is usually converted into polygonal surface meshes that often contain millions of elements. Many times this huge amount of polygonal elements comes not from the geometric complexity of the organs, arteries or tissues but from an excessive density of data offered by the scanning devices. In this perspective, even though brute force algorithms like the *marching-cubes* are still very popular, a great effort must be made to devise adaptive reconstruction algorithms that capture the essence of the geometric object at a lower computational and storing costs. For further details, see Frey **[22]** and references therein.

Formally, we can describe the problem of simplifying the initial brute-force mesh in the following way: starting with a bounded and closed set $\Omega \subset \mathbb{R}^3$ defined by its boundary Σ and assuming an initial meshing $\mathcal{M}_{ref}(\Sigma)$, possibly with an associated metric $\mathcal{H}_{ref}(\Sigma)$ to prescribe the size of elements, the goal is to construct a more suitable mesh $\mathcal{M}(\Sigma)$ for calculations, i.e. with much less elements but the same accuracy in the geometric description. The usual procedure is as follows:

1 The initial meshing, obtained by applying some brute-force method in the original medical images, is simplified and optimized within a tolerance envelope, based on a Hausdorff distance supplied by the user. This yields a geometric reference meshing $\mathcal{M}_{ref,G}(\Sigma)$.

2 A Geometric piecewise C^1 object is constructed over $\mathcal{M}_{ref,G}(\Sigma)$ defining in this way a representation of the surface Σ.

3 The metric $\mathcal{H}_{ref,G}(\Sigma)$ is modified to account for the geometry and desired smoothing effects.

4 The mesh $\mathcal{M}_{ref}(\Sigma)$ is adapted with respect to the modified metric giving the final mesh $\mathcal{M}(\Sigma)$.

As an example we present in Figure 4 the results of this procedure, starting with a very fine mesh of a human hand and ending up with two coarser meshes.

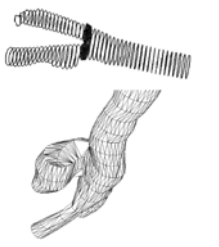

Figure 3. Surface reconstruction from a series of parallel cutting surfaces obtained from magnetic resonance. Initial lines are obtained from images using levelset methods.

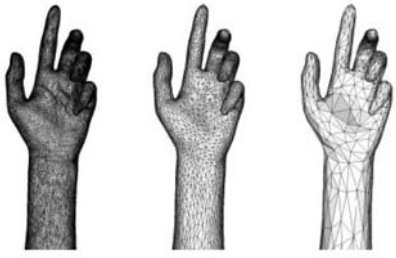

Figure 4. Example of geometric simplification. From the original brute-force discretization to a course mesh still showing the main geometric features.

4.2 Finite element method and results

The finite element method is one of the most important numerical methods to approach the solution of partial differential equations. One of its significant advantages over other methods like finite differences, finite volumes

or spectral methods is its high flexibility in dealing with irregular shaped boundaries. Different techniques have been used to solve the Navier–Stokes equations with the finite element method (see e.g. Quarteroni and Valli **[39]**, Temam **[47]**, Girault and Raviart **[23]**, Gresho and Sani **[24]**). However, the development of accurate, stable and efficient algorithms is still an important mathematical research topic.

The finite element approach requires the differential problem to be written in a weak (variational) form. Let us define two Hilbert spaces V and Q. The weak or variational formulation of our problem is obtained by multiplying the governing equations by test functions $\boldsymbol{v} \in V$ and $q \in Q$ and integrating by parts. The use of test functions can be seen as describing indirectly the solution by its effect on them. If we prescribe as boundary condition the normal stress vector $\mathbf{s} = \boldsymbol{\sigma} \cdot \mathbf{n}$ in $\Gamma = \Gamma^{in} \cup \Gamma^{out}$, together with no-slip boundary conditions in $\Omega - \Gamma$, our problem consists in finding $\boldsymbol{u} \in V$ and $p \in Q$ such that,

$$\int_\Omega \rho \left(\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u} \cdot \nabla) \cdot \boldsymbol{u} \right) \cdot \boldsymbol{v} + \int_\Omega \boldsymbol{S} : \nabla \boldsymbol{v} - \int_\Omega p \nabla \cdot \boldsymbol{v} = \int_\Omega \boldsymbol{f} \cdot \boldsymbol{v} + \int_\Gamma \mathbf{s} \cdot \boldsymbol{v}, \qquad \forall \boldsymbol{v} \in V \tag{16}$$

$$\int_\Omega q \nabla \cdot \boldsymbol{u} = 0, \qquad \forall q \in Q.$$

In the case of Newtonian or generalized Newtonian fluids the extra-stress tensor $\boldsymbol{S}$ in the second term of equation (15) is explicitly computed from the velocity gradient, through the constitutive equations (3) or (7). When dealing with a viscoelastic fluid the extra stress-tensor is obtained as the solution of a transport-like equation as in (15).

The discretization in time is done by a suitable second order trapezoidal rule / back-differentiation formula and the discretization in space uses a standard Petrov–Galerkin method (see e.g. **[39]**). To apply the Galerkin method we discretize the spatial domain Ω and introduce two families $\{V_h \mid h > 0\}$ and $\{Q_h \mid h > 0\}$ of finite element subspaces of V and Q, respectively, satisfying a compatibility condition, the so-called *discrete inf-sup* or *LBB condition*. The solution is approximated by piecewise polynomial functions on each element of the discretized domain. These polynomials must be chosen in such a way that the discrete inf-sup condition is fulfilled, otherwise the *locking* phenomenon for the velocity field or *spurious pressure modes* can occur. For instance equal order interpolation for both the velocity and pressure unknowns does not verify the inf-sup condition. The most common discretization technique is $P2 - P1$ (piecewise quadratic elements for the velocity and linear elements for the pressure) or $P1\,iso\,P2 - P1$ where

the velocity is linear over each of the four sub-elements obtained by joining the midpoints of the edges of each pressure element. Since the spaces of piecewise polynomials are of finite dimension, the substitution of the functions in the weak formulation by their expansions in the basis of the discrete spaces leads, after the numerical evaluation of the integrals, to a non-linear system of finite dimension. The resulting system is then linearized, at each time step, using an iterative Newton-like method. Error bounds can be derived for the numerical solution of this problem, based on the size of the mesh used to discretize the domain and on the type of finite elements (regularity across elements and interpolation order).

In the numerical simulations presented here we use vessels reconstructed from an MRI of the cerebral vasculature. Figures 5–9 show the original reconstruction (Figure 5) and two extracted pieces: a slightly curved vessel (Figure 6) and a bifurcation (Figure 7). In Figures 8 and 9 we display the corresponding meshes.

Figure 5. Geometric reconstruction of the cerebral vasculature.

Figure 6. Portion of the cerebral vasculature featuring a slightly curved vessel.

Figure 7. Portion of the cerebral vasculature featuring a non-planar bifurcation.

The numerical simulations were carried out in the vessel shown in Figure 6, considering pulsatile blood flow. The vessel has an average diameter of $1cm$ and approximate length of $7cm$. We compare the obtained results by modelling blood using a Newtonian and a Carreau–Yasuda model to study the non-Newtonian viscosity effects. Flow is driven by a pulsatile pressure drop between the extremities of the vessel.

In Figures 10 and 11 it is visible that both models predict approximately the same Wall Shear Stress (WSS) distribution, with the Newtonian model yielding slightly higher values as well as larger high WSS regions. This different behaviour can have a considerable impact for instance when the models are used in clinical decisions related with some pathologies such as the development of aneurysms or atherosclerotic plaque formation.

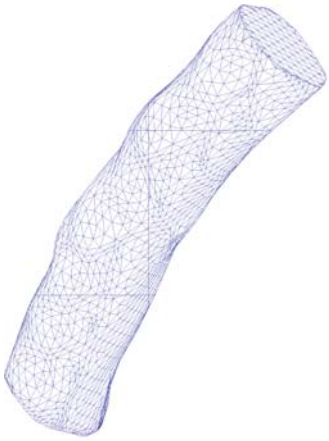

Figure 8. Meshing of the vessel shown in Figure 6.

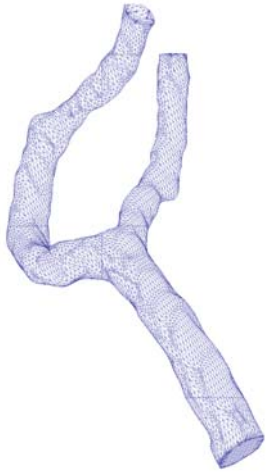

Figure 9. Meshing of the bifurcating vessel in Figure 7.

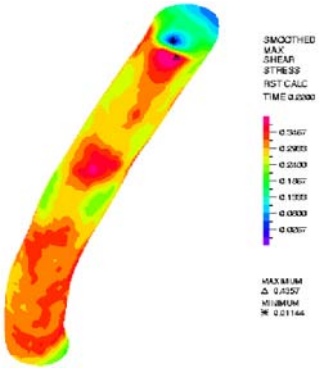

Figure 10. Wall Shear Stress (WSS) for the Newtonian model at time $t = 0.22$.

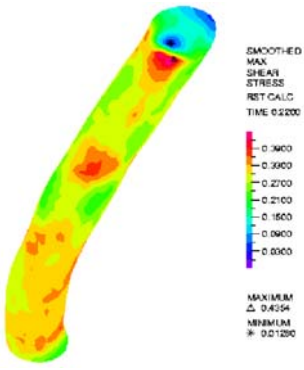

Figure 11. Wall Shear Stress (WSS) for the Carreau–Yasuda model at time $t = 0.22$.

Figure 12 represents the isovalues of the velocity field along the z axis for both Newtonian and Carreau–Yasuda models taken in three cross sections of the vessel. We observe different quantitative behaviours, in all cross sections, when the results for the two models are compared. The Carreau–Yasuda velocity shows a flattened profile (larger region of higher velocity), reaching a lower maximum value.

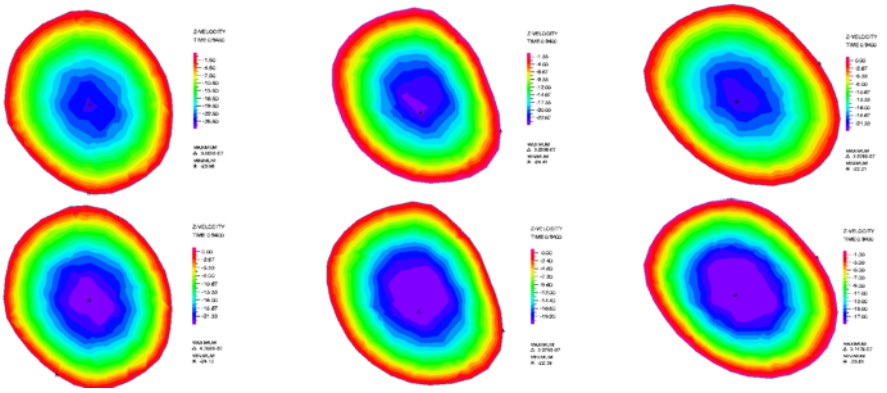

Figure 12. Isovalues of the velocity along the z axis in three different cross sections of the vessel for Newtonian model (first row) and the Carreau–Yasuda model (last row) at time $t = 0.94$.

Acknowledgments

This research has been partially supported by the Center for Mathematics and its Applications - CEMAT through FCTs funding program and by the projects POCTI/MAT/41898/2001 and HPRN-CT-2002-00270 (Research Training Network *HaeMOdel* of the European Union).

REFERENCES

[1] M. Anand, K. R. Rajagopal, A mathematical model to describe the change in the constitutive character of blood due to platelet activation, *C.R. Mécanique,* 330, 2002, pp. 557-562.

[2] M. Anand, K. Rajagopal and K. R. Rajagopal, A model incorporating some of the mechanical and biochemical factors underlying clot formation and dissolution in flowing blood, *J. of Theoretical Medicine,* 5, 2003, pp. 183-218.

[3] M. Anand and K. R. Rajagopal, A shear-thinning viscoelastic fluid model for describing the flow of blood, *Int. J. Cardiovascular Medicine and Science,* 4, 2004, pp. 59-68.

[4] N. Arada, and A. Sequeira, Strong Steady Solutions for a generalized Oldroyd-B Model with Shear-Dependent Viscosity in a Bounded Domain, *Mathematical Models & Mehods in Applied Sciences*, 13, no.9, 2003, pp. 1303-1323.

[5] O. K. Baskurt and H. J. Meiselman, Blood rheology and hemodynamics, *Seminars in Thrombosis and Hemostasis,* 29, 2003, pp. 435-450.

[6] C. G. Caro, J. M. Fitz-Gerald and R. C. Schroter, Atheroma and arterial wall shear: observation, correlation and proposal of a shear dependent mass transfer mechanism of artherogenesis, *Proc. Royal Soc. London,* 177, 1971, pp. 109–159.

[7] C. G. Caro, T. J. Pedley, R. C. Schroter and W. A. Seed, *The Mechanics of the Circulation,* Oxford University Press, Oxford, 1978.

[8] P. J. Carreau, PhD Thesis, University of Wisconsin, Madison, 1968.

[9] I. Chatziprodromoua, A. Tricolia, D. Poulikakosa and Y. Ventikos, Haemodynamics and wall remodelling of a growing cerebral aneurysm: A computational model, *Journal of Biomechanics*, accepted December 2005, in press.

[10] S. Chien, S. Usami, R. J. Dellenback, M. I. Gregersen, Blood viscosity: Influence of erythrocyte deformation, *Science,* 157 (3790), 1967, pp. 827-829.

[11] S. Chien, S. Usami, R. J. Dellenback, M. I. Gregersen, Blood viscosity: Influence of erythrocyte aggregation, *Science,* 157 (3790), 1967, pp. 829-831.

[12] S. Chien, S. Usami, R. J. Dellenback, M. I. Gregersen, Shear-dependent deformation of erythrocytes in rheology of human blood, *American Journal of Physiology,* 219, 1970, pp. 136-142.

[13] Y. I. Cho and K. R. Kensey, Effects of the non-Newtonian viscosity of blood on flows in a diseased arterial vessel. Part I: Steady flows, *Biorheology*, 28, 1991, pp. 241-262.

[14] G. R, Cokelet, The rheology of human blood. In: Y. C. Fung and M. Anliker (Eds.), *Biomechanics: its foundations and objectives,*, Ch. 4, Prentice Hall, 1972.

[15] A. L. Copley, The rheology of blood. A survey, *J. Colloid Sci.,* 7, 1952, pp. 323-333.

[16] A. L. Copley and G. V. F. Seaman, The meaning of the terms rheology, biorheology and hemorheology, *Clinical Hemorheology,* 1, 1981, pp. 117-119.

[17] V. Cristini and G. S. Kassab, Computer modeling of red blood cell rheology in the microcirculation: a brief overview, *Annals of Biomedical Engineering,* 33, n.12, 2005, pp. 1724-1727.

[18] M. M. Cross, Rheology of non-Newtonian fluids: a new flow equation for pseudo-plastic systems, *J. Colloid Sci.,* 20, 1965, pp. 417-437.

[19] R. Fåhraeus, Die Strömungsverhältnisse und die Verteilung der Blutzellen im Gefässsystem, *Klin. Wschr.,* 7, 1928, pp. 100-106.

[20] R. Fåhraeus and T. Lindqvist, The viscosity of blood in narrow capillary tubes, Am. J. Physiol. 96. 1931, pp. 562-568.

[21] A. L. Fogelson, Continuum models of platelet aggregation: formulation and mechanical properties, *SIAM J. Appl. Math.,* 52, 1992, 1089-1110.

[22] P. J. Frey, Génération et adaptation de maillages de surfaces à partir de données anatomiques discrètes, *Rapport de Recherche,* 4764, INRIA, 2003.

[23] V. Girault and P.-A. Raviart, *Finite Element Methods for the navier-Stokes Equations,* Springer-Verlag Berlin, Heidelberg, New York, Tokyo, 1986.

[24] P. M. Gresho and R. L. Sani, *Incompressible Flow and the Finite Element Method,* Vol.2, Jphn Wiley and Sons, Chichester, 2000.

[25] C. R. Huang, N. Siskovic, R. W. Robertson, W. Fabisiak, E. H. Smith-Berg and A. L. Copley, Quantitative characterization of thixotropy of whole human blood, *Biorheology,* 12, 1975, pp. 279-282.

[26] R. Keunings, A survey of computational rheology, in: *Proceedings of the XIIIth International Congress on Rheology* (D.M. Binding *et al.* ed.), British Soc. Rheol., 1, 2000, pp. 7-14.

[27] A. Kuharsky, *Mathematical modeling of blood coagulation,* PhD Thesis, Univ. of Utah, 1998.

[28] A. Kuharsky, A. L. Fogelson, Surface-mediated control of blood coagulation: the role of binding site densities and platelet deposition, *Biophys. J.,* 80 (3), 2001, pp. 1050-1074.

[29] D. O. Lowe, *Clinical Blood Rheology,* Vol. I, II, CRC Press, Boca Raton, Florida, 1998.

[30] D. E. McMillan, J. Strigberger and N. G. Utterback, Rapidly recovered transient flow resistance: a newly discovered property of blood, *American Journal of Physiology,* 253, pp. 919-926.

[31] R. G. Owens and T. N. Phillips, *Computational Rheology,* Imperial College Press/World Scientific, London, UK, 2002.

[32] R. G. Owens, A new microstructure-based constitutive model for human blood, *J. Non-Newtonian Fluid Mech.,*, 2006, to appear.

[33] M. J. Perko, Duplex Ultrasound for Assessment of Superior Mesenteric Artery Blood Flow, *European Journal of Vascular and Endovascular Surgery,* 21, 2001, pp. 106-117.

[34] K. Perktold and M. Prosi, Computational models of arterial flow and mass transport, in:*Cardiovascular Fluid Mechanics* (G. Pedrizzetti, K. Perktold, Eds.), CISM Courses and Lectures n.446, Springer-Verlag, pp. 73-136, 2003.

[35] W. M. Phillips, S. Deutsch, Towards a constitutive equation for blood, *Biorheology,* 12(6), 1975, pp. 383-389.

[36] A. S. Popel and P. C. Johnson, Microcirculation and hemorheology, *Annu. Rev. Fluid Mech.,* 37, 2005, pp. 43-69.

[37] A. R. Pries and T. W. Secomb, Rheology of the microcirculation, *Clinical Hemorheology and Microcirculation,* 29, 2003, pp. 143-148.

[38] D. A. Quemada, A non-linear Maxwell model of biofluids - Application to normal blood, *Biorheology,* 30(3-4), 1993, pp. 253-265.

[39] A. Quarteroni and A. Valli, *Numerical Approximation of Partial Differential Equations*, Springer-Verlag, Heidelberg, 1994.

[40] K. R. Rajagopal, A. Srinivasa, A thermodynamic framework for rate type fluid models, *J. of Non-Newtonian Fluid Mech.,* 88, 2000, pp. 207-228.

[41] G. Rappitsch, K. Perktold and E. Pernkopf, Numerical modelling of shear-dependent mass transfer in large arteries, *Int. J. Numer. Meth. Fluids,* 25, 1997, pp. 847-857.

[42] M. Renardy, Existence of slow steady flows of viscoelastic fluids with a differential constitutive equation, *Z. Angew. Math. Mech.,* 65, 1985, pp. 449-451.

[43] M. Renardy, *Mathematical Analysis of Viscoelastic Flows,* CBMS 73, SIAM, Philadelphia, 2000.

[44] G. W. Scott-Blair, An equation for the flow of blood, plasma and serum through glass capillaries, *Nature,* 183, 1959, pp. 613-614.

[45] R. Tabrizchi and M. K. Pugsley, Methods of blood flow measurement in the arterial circulatory system, *Journal of Pharmacological and Toxicological Methods,* 44 (2), 2000, pp. 375-384.

[46] C. A. Taylor, M. T. Draney, J. P. Ku, D. Parker, B. N. Steele, K. Wang, C. K. Zarins, Predictive medicine: Computational techniques in therapeutic decision–making, *Computed Aided Surgery,* 4(5), 1999, pp.231-247.

[47] R. Temam, *Navier–Stokes Equations, Theory and Numerical Analysis,* North Holland, Amsterdam, 1984.

[48] G. B. Thurston, Viscoelasticity of human blood, *Biophys. J.,* 12, 1972, 1205-1217.

[49] G. B. Thurston, Rheological parameters for the viscosity, viscoelasticity and thixotropy of blood, *Biorheology,* 16, 1979, pp. 149-162.

[50] G. B. Thurston, Light transmission through blood in oscillatory flow, *Biorheology,* 27, 1990, pp. 685-700.

[51] G. B. Thurston, Non-Newtonian viscosity of human blood: flow-induced changes in microstructure, *Biorheology,* 31(2), 1994, pp. 179-192.

[52] R. Unterhinninghofen, J. Albers, W. Hosch, C. Vahl and R. Dillmann, Flow quantification from time-resolved MRI vector fields, *International Congress Series,* 1281, 2005, pp. 126-130.

[53] G. Vlastos, D. Lerche, B. Koch, The superimposition of steady and oscillatory shear and its effect on the viscoelasticity of human blood and a blood-like model fluid, *Biorheology,* 34(1), 1997, pp. 19-36.

[54] F. J. Walburn, D. J. Schneck, A constitutive equation for whole human blood, *Biorheology,* 13, 1976, pp. 201-210.

[55] N. T. Wang, A. L. Fogelson, Computational methods for continuum models of platelet aggregation, *J. Comput. Phys.,* 151, 1999, pp. 649-675.

[56] B. J. B. M. Wolters, M. C. M. Rutten, G. W. H. Schurink, U. Kose, J. de Hart and F. N. van de Vosse, A patient-specific computational model of fluid-structure interaction in abdominal aortic aneurysms, *Medical Engineering & Physics,* 27, 2005, pp. 871-883.

[57] K. K. Yelesvarapu, M. V. Kameneva, K. R. Rajagopal, J. F. Antaki, The flow of blood in tubes: theory and experiment, *Mech. Res. Comm,* 25 (3), 1998, pp. 257-262.

[58] J.-B. Zhang and Z.-B. Kuang, Study on blood constitutive parameters in different blood constitutive equations, *J. Biomechanics,* 33, 2000, pp. 355-360.